

Children with Cancer as Participants in End-of-Life Research

by

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Abstract

Children with cancer participate in research towards the end of life (EOL), including early phase anticancer treatment trials and palliative care studies exploring topics like decision making and communication. These studies advance pediatric oncology, improving cancer therapy and supportive care. However, ethical concerns have been raised regarding family understanding of the purpose and benefits of studies, and participant burdens.

I sought to address knowledge gaps about EOL research by conducting three studies. First, I performed a retrospective cohort study, using CYP-C data* to describe the population of Canadian children who participated in early phase cancer therapy studies towards the EOL. 4.5% of children who died during this period participated in trials. Participation was associated with a brain tumor diagnosis, treatment in a major early phase study center, previous trial participation, and higher socioeconomic status.

*CYP-C refers to the Cancer in Young People in Cancer, population-based database

Second, I performed a systematic review including 24 studies that explored stakeholder perspectives about children's participation in EOL research. However, results were limited, as studies including health professionals (HPs) mostly focused on physicians, and used survey methodology, limiting the depth of their findings. There was a paucity of literature about palliative care research.

In the third study, I used interpretive description to explore HPs' perspectives about EOL research-related decision-making, across interprofessional roles. My findings indicated that these decisions were made in an emotionally charged context that influenced decision making. HPs experienced dialectic tensions in a minority of cases, for example, a tension between granting parents the autonomy to choose study enrollment for their children but wanting to protect those children from the adverse consequences of participation. These tensions were experienced as ethical struggles and sometimes, moral distress. HPs with limited involvement in decision making but who implemented decisions, particularly struggled.

These results indicate that a small proportion of children participate in early phase anticancer treatment trials towards the EOL. Socioeconomic and other factors are associated with participation. HPs struggle with certain cases of EOL decision making, sometimes experiencing this as moral distress. Future research should explore potential barriers to trial participation and find ways to better support HPs involved in making and implementing decisions about studies.

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Chapter 1

Introduction

1 Background

1.1 End-of-Life Research in Pediatric Oncology

Each year, approximately 900 Canadian children under fifteen years of age are diagnosed with cancer¹. Survival rates have increased dramatically over the past 40 years². However, 16% of patients still die of their disease or its treatment². In Canada, this means that around 150 children die of cancer each year³. These children may participate in end-of-life (EOL) research prior to death.

EOL research plays a vital role in pediatric oncology, generating knowledge needed to improve the quality of cancer care⁴. EOL research falls under two broad categories: i) studies of cancer-directed treatments, including early phase (phase I/II) trials of anticancer therapies, and ii) palliative and supportive care research. As described by Health Canada, these trials are intended to provide information about drug dosing, side effects and initial information about drug efficacy⁵. Early phase trials can explore any kind of therapy including anticancer *and* palliative or supportive care therapies. However, for the purposes of this thesis, I will restrict my use of the term ‘early phase’ or ‘phase I/II studies’ to describe trials of anticancer therapies. I will include all palliative and supportive care research that occurs towards EOL under the category of ‘palliative care’ research, regardless of the phase of study.

Participants in pediatric oncology early phase studies are usually children with relapsed or progressive cancers who do not have a realistic chance of cure with conventional therapy. The purpose of these studies is to provide initial information on novel anticancer treatments or combinations of treatments, which (if successful) will go on to be tested in future research⁶. Although children, families, and health professionals (HPs) may choose early phase study enrollment hoping for the patient’s personal benefit, the primary aim of these studies is to produce generalizable knowledge that will improve outcomes for future patients⁷⁻⁹.

Pediatric oncology palliative care research is a broad field of study that aims to improve the quality of palliative care provided to children with cancer. Palliative care aims to mitigate the

physical and psychological suffering experienced by children with cancer, particularly towards the EOL¹⁰⁻¹². Thus, palliative care research may address a wide range of issues including symptom prevalence and management, EOL preferences, decision making, and communication, for example, between children and parents, or families and HPs.

Despite the complexity of providing palliative care to children, including children with cancer, there is a lack of research evidence that can be used to guide practice^{13,14}. The Institute of Medicine and the American Academy of Pediatrics are among the major health organizations that have highlighted deficiencies in the evidence base for pediatric palliative care^{15,16}. Two recent Delphi studies invited parents of children requiring palliative care, HPs, and researchers to identify pediatric palliative care research priorities^{14,17}. These studies identified several areas including decision making, symptom management, and care coordination as key priorities for future research. Similarly, Hilden *et al* noted deficiencies in the evidence base for *every* aspect of pediatric oncology palliative care¹⁸. Furthermore, they noted that research in several priority areas, including decision making would be “of direct benefit in the treatment of dying children”.

There are limited data describing the number of children who directly participate in EOL research. Although there is increasing awareness of the need for palliative care research in pediatric oncology, these studies are still uncommon, and there is no empirical evidence describing rates of participation¹⁸⁻²⁰. In contrast, it is not uncommon for children with cancer to participate in early phase anticancer treatment studies²¹. Single institution case series have reported the characteristics and outcomes of small cohorts of children participating in early phase anticancer trials²²⁻²⁴. However, there are no published population-based data to describe these children and limited data to describe access to trials²⁵.

Despite the potential contributions that EOL research can make, ethical concerns are often raised that this research may inappropriately burden vulnerable participants, who are perceived to have a low chance of benefiting from research participation but who are thought to be exposed to potential risk by their enrollment²⁶. Specific to early phase studies of anticancer therapies, is the concern that patients may participate because of therapeutic misconception, the mistaken belief that the primary aim of research is to benefit the patient, rather than to create generalizable knowledge^{8,26-29}. A related concern is that patients or their relatives may overestimate the

likelihood that they will personally benefit from their research trial participation, a concept known as therapeutic optimism⁹. These concerns may have several implications for the conduct of trials, most importantly that children and their families may participate in research without providing consent that is truly informed.

Regarding palliative care research, research ethics boards (REBs) may show reluctance to approve studies, and funding bodies may be hesitant to support studies particularly if they involve patients coming towards the EOL^{27,30}. When studies succeed in gaining REB approval to be conducted, treating physicians and other HPs may fail to approach patients or families to offer study participation, limiting recruitment^{30,31}. This phenomenon, known as ‘gatekeeping’, may be motivated by fears that studies could be burdensome to vulnerable participants, that studies could take up too much valuable time from participants, or perceptions that participants may have little to gain from enrollment^{30,32,33}. This phenomenon may be problematic for research by both slowing down recruitment as well as possibly introducing selection bias if patterns of non-enrollment are systematic¹⁹.

Despite the challenges in conducting pediatric palliative care research, it should be noted that there may be beneficial effects of participating for both the parents and children involved. Studies of bereaved parents who have participated in research interviews (after the death of their child) have shown that they perceived their participation to be beneficial to them, even therapeutic, despite being psychologically difficult³⁴. Other authors have noted that children and families may find legacy and meaning in an altruistic act of participating in research that could benefit future patients^{19,30,35}.

Given the potential contribution of EOL research to the advancement of pediatric oncology, the benefits and harms that families may perceive, and the challenges and ethical questions around the conduct of this research, it is important to understand the perspectives of relevant stakeholders. While prior studies have explored parents’ experiences and views, fewer studies included children with cancer³⁶⁻³⁹. Regarding HPs’ views, previous studies primarily focused on the perspectives of physicians, and to a lesser extent, nurses, about enrollment in phase I/II studies⁴⁰⁻⁴². However, they do not provide in-depth description of how complex decisions about trial enrollment are made and fail to describe how these decisions are experienced by HPs in

other roles within interprofessional teams. There is more limited information available regarding parent, child, or HP perceptions of palliative care research involving children with cancer^{19,30,32}.

1.2 Research Approach

In this thesis, I explored research-related decision making for children with cancer towards the EOL. I performed three linked studies: namely a quantitative study using a population-based cancer registry, a systematic review, and a single institution qualitative study.

These studies addressed the following primary research questions (listed by study):

1. Phase I/II Study Enrollment in Canadian Children with Cancer Proximal to Death: A Population-Based Retrospective Cohort Study

What proportion of Canadian children who died of cancer were enrolled in an early phase trial of anticancer treatment towards the EOL?

What were the characteristics of this patient group and the studies they participated in and how did study participation affect their EOL trajectories?

2. End-of-Life Childhood Cancer Research: A Systematic Review

What are the perceptions and experiences of children with cancer, their parents and the HPs who/ treat them on the enrollment of children with cancer in phase I or other research studies at the EOL?

3. Ethical Issues and Interprofessional Tensions: Making Decisions about Research for Children with Cancer at the End of Life: A Qualitative Study

How do HPs in different roles view EOL research studies involving children with cancer as participants?

How are decisions about research made within interprofessional teams?

How do team members perceive and navigate ethical and other concerns regarding research?

How are perspectives influenced by the type of research study (early phase studies of anticancer treatment) vs palliative care research)?

Given the nature of the evidence gaps that I chose to address, I opted to take a multiple methods approach. Quantitative methods were necessary to characterize the population of Canadian children who participated in EOL early phase anticancer studies, and explore the influence of demographic, disease and treatment-related characteristics on study participation. In contrast, to describe the existing literature about children's, parents', and HPs' perspectives and experiences on EOL research, a qualitative approach was appropriate. Similarly, qualitative methods were necessary to provide a rich description of the complex and nuanced decision-making that occurs as interprofessional teams of HPs consider EOL research participation for their patients.

Describing the population who take part in research, and the research-related decision-making process provides a starting point towards future work that will study how to support children, families, and HPs through this challenging process.

Chapter 2

2 Early Phase Study Enrollment in Canadian Children with Cancer Near End of Life: A Retrospective Cohort Study

2.1 Abstract

Purpose: Children with cancer may participate in early phase (phase I/II) trials of anticancer therapy towards the end of life (EOL) but we know little about their experience. Our primary objectives were 1) to describe the proportion of Canadian children with cancer who participate in early phase anticancer studies in the EOL period (last 90 days of life); 2) explore the relationships between demographic, disease and treatment-related factors and study enrollment.

Patients and Methods: This retrospective cohort study used data from the Cancer in Young People in Canada (CYP-C) database, a national population-based registry. We included Canadian children and adolescents with cancer aged 0-20 years at death and who died between 2001 and 2021. We performed logistic regression analyses to explore the relationships between demographic, disease and treatment-related factors and study enrollment.

Results: Of 3,125 children and adolescents who died, 140 (4.5%) met study criteria. Patients in the lowest census-based income quintiles (quintiles 1-2) enrolled less frequently than those in the highest quintiles (3-5) (odds ratio (OR) 0.56, 95% confidence interval (CI) 0.37-0.84). Patients with leukemia or lymphoma (OR=0.54, 95%CI 0.33-0.87) or a solid tumor (OR=0.48, 95%CI 0.29-0.79) enrolled less frequently than those with central nervous system tumors. Previous trial enrollment (OR=3.02, CI 2.43-3.77), and initial treatment in a major early phase study center (OR=1.65, 95%CI 1.14-2.4) were associated with early phase study enrollment.

Conclusion: A small proportion of children and adolescents participate in early phase trials towards the EOL. Lower socioeconomic status, specific cancer diagnoses, and treatment outside of a major early phase center are associated with non-enrollment. Clinicians, researchers, and policy developers should consider the impact that socioeconomic and other factors may have on

patients' ability to access studies and explore ways to ensure equitable access for diverse patient populations.

2.2 Introduction

Major improvements in childhood cancer survival have been attributed to the participation of pediatric patients in clinical trials^{43,44}. Early phase (phase I and II) trials of anticancer therapies, make an important contribution to childhood cancer research⁴. These studies are usually designed to provide information on dose-limiting toxicities, recommended drug doses, and determine first signals of efficacy, to be tested in future research⁶.

Study participants typically have relapsed, refractory or progressive cancers. Eligibility criteria usually require patients to have exhausted standard therapeutic options and to have a life expectancy of 2 to 3 months at enrollment, though this is often difficult to predict. Children therefore commonly participate in trials close to the end of life (EOL).

Several studies have explored clinical trial enrollment patterns for children newly diagnosed with cancer⁴⁵⁻⁴⁸. However, there is limited information regarding enrollment for pediatric patients in early phase trials of anticancer treatments. Although small case series and surveys have reported the characteristics, outcomes and motivations of children and their parents in participating in early phase studies, there are no published population-based data describing these patients^{22-24,49,50}.

Canadian children with cancer can access early phase studies via a universal healthcare system which is free of cost at the point of use and organized and provided by individual provinces. However, early phase trials are typically only available at a small number of centers due to the expertise and infrastructure needed for study administration, with the largest centers located in Vancouver, Montreal, and Toronto. This means that it may be challenging for patients to access trials unless they are treated at a center offering those trials. While other families may travel to participate in studies, factors like distance, administrative hurdles, financial aspects, such as the costs of accommodation, travel, or forgoing employment, may limit families' ability to do so²⁵.

Our primary objective was to describe the proportion of Canadian children with cancer who participated in early phase (phase I/II) trials of anticancer treatments at the EOL, defined as their final 90 days. Our second objective was to explore the relationship between demographic, disease and treatment-related factors and early phase study enrollment. We were particularly interested to understand how challenges in accessing trials due to financial factors and care delivery may influence participation. A third objective was to describe the early phase treatment trials that patients were enrolled on at EOL. Fourthly, we sought to describe the EOL course of enrolled patients.

2.3 Methods

Ethical approval was granted by the Research Ethics Board of The Hospital for Sick Children. Given that this was a retrospective secondary analysis, the requirement for informed consent was waived.

2.3.1 Study Population

We included children and adolescents who: a) were aged under 19 years at cancer diagnosis; b) died between April 1st, 2001 (90 days after database inception) to July 8th, 2021; c) died aged 20 years or younger; d) were diagnosed and treated in one of the seventeen Canadian tertiary pediatric oncology centers, and data were included in the CYP-C database; and e) had a cancer diagnosis listed in the International Classification of Childhood Cancer (ICCC)⁵¹. The ICCC includes malignant cancers of childhood and non-malignant tumors of the brain and spine. We excluded patients who died after the age of 20, since they are usually managed in adult oncology centers, thus data are not reliably available in CYP-C.

2.3.2 Data Sources

CYP-C is a Canadian pediatric oncology population-based database. It aims to collect information on all children and adolescents (aged under 19 years) with cancer treated in the 17 Canadian tertiary pediatric oncology centers. The 12 non-Ontario centers input data directly into CYP-C, whereas the 5 Ontario centers submit data via the Pediatric Oncology Group of Ontario

Networked Information System (POGONIS), which captures similar data. CYP-C captures data for children for the first five years after initial diagnosis, and after the diagnosis of any subsequent cancer, whereas POGONIS captures data up until death.

Multiple methods are used to ensure the accuracy of CYP-C data. Data is abstracted by trained staff; data managers receive regular training, and non-Ontario data is audited⁵². A waiver of participant consent for data collection in CYP-C contributes to data completeness. Data collected include demographic, diagnostic, and treatment details, relapse, and vital status. CYP-C documents whether a patient was enrolled on any therapeutic clinical trial and documents trial names or numbers.

2.3.3 Procedures

Treatment plans administered during the EOL phase were identified from CYP-C. EOL was defined as the 90-day period before death. Trial details were then obtained from www.clinicaltrials.gov, supplemented by information from study protocols, publications, and pediatric oncology centers. An investigator (FH) collected the following information about plans: a) whether the patient was enrolled on a clinical trial of anticancer therapy; b) the phase of any trial; c) whether the protocol included conventional chemotherapy, targeted agents, immunomodulators or antiangiogenic agents; d) the route of any agents given (oral, intravenous, intrathecal or intramuscular); e) whether the protocol included chimeric antigen T-cell receptor, (CART cell), or metaiodobenzylguanidine, (¹³¹I-MIBG) therapy; and f) whether pharmacokinetic or biomarker blood tests were included in the protocol. Drug doses were not collected.

2.3.4 Outcomes

The primary outcome was enrollment in an early phase anticancer treatment trial during the EOL period. We defined enrollment, as being enrolled on a phase I or II trial of anticancer therapy at any point during the 90-day window before death. The first day of enrollment may have been prior to or during the 90-day window. CYP-C provided dates of enrollment and study completion. CYP-C does not categorize the phase of trial. An investigator (FH) collected information about the phase of trial from www.clinicaltrials.gov⁵³. When this information was unavailable via www.clinicaltrials.gov, FH used supplementary information from study

protocols, publications, and pediatric oncology centers to identify the phase. If no phase was identified, Health Canada definitions of the phases of clinical trials were used to categorize studies⁵. One study that had both phase II and III components, was classified as a phase II study, since we could not identify which component the patient was enrolled in.

Secondary outcomes included details of treatments administered as part of trials in the EOL period, as above. Additional secondary outcomes were available from CYP-C including completion of trial protocols and reasons for non-completion. A final set of secondary outcomes was chosen to describe the EOL course: a) courses of radiation and hematopoietic cell transplantation (HCT); b) the intent of any courses of radiation; c) the incidence of ≥ 3 grade (hematological and non-hematological) adverse events, as defined by the version of the Common Terminology Criteria for Adverse Events in place at the time of the event; and e) the total number of days of hospitalization⁵⁴. Radiation, HCT and complications were all categorized as dichotomous variables. We restricted our description of certain outcomes (intent of radiation, complications and hospitalization) to non-Ontario CYP-C patients, as complete data were not available for POGO patients.

2.3.5 Covariates

Covariates were those available in CYP-C. The following factors were explored: demographic factors (age at death, sex, race, urban dwelling at diagnosis and socioeconomic status), disease-related factors (last cancer diagnosis, metastatic disease at last cancer diagnosis, history of relapse prior to the EOL period, time from first diagnosis to death), and treatment-related factors (previous clinical trial enrollment, radiation therapy and HCT (i.e. prior to the EOL period)) and initial treatment in a 'major early phase study center', (MEPSC)). These factors were chosen as they may influence both the desire of patients and families and their ability to access early phase anticancer treatment trials at EOL^{45,47,55-57}.

CYP-C collects 6-digit postal codes at the time of diagnosis for patients across Canada except British Columbia, where 3-digit postal codes are collected. Urban dwelling was classified by CYP-C using each patient's postal code. CYP-C used postal code conversion software to calculate income quintiles adjusted for locoregional differences and household size as described previously⁵⁸. We used income quintile as a proxy for socioeconomic status, creating a

dichotomous variable: higher (quintiles 3-5), and lower (quintiles 1-2). We created the covariate ‘initial treatment in a MEPSC’ as a proxy for being treated in a center with the greatest access to early phase cancer treatment studies. There are multiple possible definitions of an MEPSC. We defined The Hospital for Sick Children, Toronto; BC Children’s Hospital, Vancouver; and Centre Hospitalier Universitaire Sainte-Justine, Montreal, as MEPSCs since they offer the largest portfolios of pediatric phase I/II trials across Canada.

2.3.6 Statistical Analyses:

The primary objective was to describe the proportion of Canadian children with cancer who were enrolled in an early phase anticancer treatment study in the EOL period. This analysis was descriptive.

For our secondary objective, we performed univariable logistic regression to describe the relationship between patient, demographic and treatment-related factors, and enrollment in an early phase anticancer trial during the EOL period. We calculated odds ratios (OR) with 95% confidence intervals (CI) to describe the relationship between evaluated factors and enrollment. For multivariable modelling, we included factors with a p-value of 0.25 or less.

We used complete case analysis for regression modeling. We then performed a secondary analysis using the MICE (Multiple Imputation using Chained Equations) package in R software to replace missing values⁵⁹. We created 20 imputed datasets including all covariates in our imputation model. Logistic regression was used to impute missing values, which were all from categorical variables.

Our initial analyses included all deaths. Since patient data is entered into CYP-C from two different sources i.e., directly into CYP-C or via POGONIS, we performed a subgroup analysis stratified by source.

Our final objectives were to describe the clinical trials that patients were enrolled on at EOL, and their EOL course. These analyses were descriptive. We excluded hospitalizations, complications, courses of radiotherapy, HCT, and trial enrollments where both start and end dates were missing. We used median imputation to calculate the length of hospitalization in the EOL period where dates of admission or discharge were missing or incorrect (e.g., discharge after death).

Our analyses were performed in R, were two-tailed, and used a p-value<0.05 to define statistical significance⁵⁹. This report was written with reference to The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement⁶⁰.

2.4 Results

Figure 2.1 shows the flow diagram of patient identification and selection. Of 3,334 children who died during the study period, 3,125 were included in the analyses. We were unable to identify the phase of one study administered at the EOL, and categorized this patient as not enrolled in an early phase trial.

One hundred and forty, (4.5%) of patients were enrolled in an early phase anticancer treatment trial in the EOL period. For eighty-four of these patients, (60%), study enrollment first began prior to the EOL period (i.e., more than 90 days before death).

Table 2.1 shows the demographic, disease, and treatment-related characteristics of the cohort, stratified by enrollment in an early phase study during EOL. Univariate analyses revealed that enrolled patients were more likely to have a central nervous system (CNS) tumor and non-metastatic disease at last cancer diagnosis (Table 2.2). Enrolled patients were more likely to have received radiotherapy, to have enrolled in another clinical trial before EOL and to have received upfront therapy in an MEPS. Enrollment was less common in patients with solid tumors and with lower census-based income quintiles.

On multivariate analysis, patients with leukemia or lymphoma (OR=0.54, 95%CI 0.33-0.87) or a solid tumor (OR=0.48, 95%CI 0.29-0.79) enrolled less frequently than those with central nervous system tumors. Previous trial enrollment (OR=3.02, CI 2.43-3.77), and initial treatment in a major early phase study center (OR=1.65, 95%CI 1.14-2.4) were associated with enrollment. Patients in the lowest income quintiles (quintiles 1-2) enrolled less frequently than those in the highest quintiles (3-5) (odds ratio (OR) 0.56, 95% confidence interval (CI) 0.37-0.84) (Table 2.3).

Complete data were available for regression modeling for 2,918 (93.3.1%) patients. Similar results were obtained when MICE was used to address missing data. Our subgroup analysis, stratified by source (CYP-C or POGONIS) did not suggest differences in effect sizes between subgroups for all covariates, except sex (Supplementary Table 2.1). To determine if the impact of source on enrollment differed by sex, we evaluated an interaction term in a multivariable model including sex and data source. The p-value for the interaction term was 0.312, consistent with a similar effect for both sexes.

Table 2.4 provides a description of the study protocols used in the EOL period for patients enrolled in early phase trials. For the 140 enrolled patients, 142 trial registrations were documented, as some patients enrolled on more than one study. Chemotherapy agents included in early phase trials were most commonly conventional chemotherapy medications (76.1% of trials). However, targeted (34.5%), immunomodulatory (14.8%) and antiangiogenic agents (4.9%) were also included. Sixty-three percent of trial plans included at least one oral agent, with 40.8% of plans using only the oral route for chemotherapy or other agents. Nearly 60% included one or more intravenous chemotherapy agent. Nearly 70% of early phase trial registrations were on studies that included blood pharmacokinetic or biomarker testing. Non-completion of a treatment plan was common, with 88% of enrolled patients terminating their trial participation early. Reasons for non-completion were available for 65% of those patients, with progression or relapse of disease (42.4%) or death (17.6%) being the most common reasons documented. Toxicity was the documented cause of non-completion in <6 cases.

Of the 2,985 patients who were not enrolled on an early phase study in the EOL period, 161 (5.3%) were treated 'as per' phase I/II study protocols, meaning that they received study treatments according to phase I/II protocols without being enrolled as research study participants. Table 2.5 describes the EOL course. Hospitalization and complications data were available for 59% of enrolled patients who were hospitalized for a median of nine days in the EOL period, with 13.6% experiencing a ≥ 3 grade adverse event. The intent of therapy was documented for 740 EOL radiation courses as: palliative (552 courses, 75%), curative (182 courses, 25%), and other/not available (6 courses, <1%).

2.5 Discussion

We found that 4.5% of children and young people who died of cancer were enrolled in early phase studies during the EOL period. As we are unaware of other population-based studies that examine early phase trial enrollment at EOL, we cannot compare our results with those from other geographic regions. However, Pole *et al* explored research study participation for newly diagnosed Canadian children with cancer⁴⁵. While they included any phase of clinical trial, it is interesting to compare their findings to ours. They identified that 27.5% of children were enrolled in interventional clinical trials. Given the reduced possibility of therapeutic benefit, it is unsurprising that a lower number of children enroll in studies at EOL than diagnosis.

Of note, despite inclusion criteria for early phase trials that typically include an expected life expectancy of at least three months, 40% of study enrollments began within the last 90 days of life. This may suggest that oncologists or researchers overestimate patient prognoses, or that health professional or family preferences favor study enrollment. Late enrollments may also explain the high rate of study non-completion, with most patients not completing their treatment protocol.

It is reassuring that while rates of non-completion were high, the number of days of hospitalization and the incidence of adverse events were low and toxicity was a rare cause of study termination. Similarly, in a small case series, Morgenstern *et al* identified high rates of non-completion noting that most early terminations were due to disease progression, rather than toxicity²².

It is notable that the proportion of patients who were enrolled in early phase trials was slightly lower than the proportion who were non-enrolled, but treated ‘as per’, an early phase trial in the EOL period. This occurred, presumably, after results of early phase studies were known, and likely reflects the use of investigational therapies to provide additional treatment options for patients without other curative options. While it is understandable that families and HPs may utilize these investigational therapies in the absence of other proven options, this is of some concern given that trial treatments would not have been studied in larger randomized studies at the time of use, possibly exposing patients to ineffective treatments or side effects.

A brain tumor diagnosis was more commonly associated with EOL study enrollment than a diagnosis of solid tumor, leukemia, or lymphoma. Several single institution case series showed similar enrollment patterns^{22,23}. This may reflect increased availability of trials for specific diagnoses or other factors such as rapid progression of relapsed or refractory leukemias.

Pole identified that greater distance from home to a tertiary center was associated with non-enrollment in clinical trials⁵. While we did not include this variable, we identified an association between upfront treatment at an MEPSC and subsequent enrollment in an early phase trial during EOL. This association may reflect ease of access to trials due to geography. However, it may also reflect other factors, such as family preferences to continue treatment without moving to another oncology center, a culture of promoting early phase studies in MEPSCs, and a lack of administrative or funding barriers for families choosing enrollment who are already treated in these centers⁶¹.

It was interesting to note that prior enrollment in a clinical trial was associated with enrollment at the EOL. It may be that families who are open to research participation at diagnosis remain open at EOL, or that prior experience with research increases family willingness or desire to participate in studies at EOL. It may also be that patients who receive their upfront therapy at MEPSCs have increased access to open trials at all points on their trajectory. This is worthwhile noting, as efforts to increase enrollment rates for newly diagnosed patients may have a trickle-down effect, increasing enrollment at EOL.

In contrast to Pole, but like many adult oncology studies, we identified a statistically significant association between study enrollment and socioeconomic status^{45,62-64}. Given the financial strains faced by parents of children with cancer, particularly at the EOL, it is possible and concerning that finances may prevent enrollment, especially for families needing to travel for treatment^{65,66}. Alternatively, parental education and literacy may contribute to the association between enrollment and socioeconomic status. Perhaps less likely, is the possibility that EOL care preferences vary for families from different socioeconomic backgrounds.

2.5.1 Strengths and limitations

Strengths of this study include the population-based approach, the 20-year span and relatively large sample size. This approach increases the generalizability of our findings, compared to previous studies.

However, several limitations should be noted. First, a single author extracted data and categorized the phase of study. However, given the processes used to categorize studies, we believe our approach was robust. Second, by describing a broad patient group over a 20-year period, we created a heterogeneous cohort. Given the small number of enrolled patients, we did not assess changes in enrollment over time. However, it is possible that clinical care, enrollment patterns and early phase trials may have changed during this period. Third, we created a variable, ‘initial treatment in an MEPSC’, to explore possible increased access to early phase studies in centers with the largest trial portfolios. However, another definition of an ‘MEPSC’ may have yielded different results. Fourth, our findings may not be generalizable in other health care systems, depending on how care and early phase trials are provided. Finally, we were unable to fully explore the implications of trial participation on participants’ EOL experience. Variables such as referral to a specialist palliative care team, location of death, intensive care admission at EOL etc., are not captured by CYP-C, nor are perspectives about EOL care or patient reported outcomes, including measures of quality of life.

2.6 Conclusions

In conclusion, 4.5% of Canadian children with cancer were enrolled in an early phase study during EOL. Cancer-specific, treatment and sociodemographic features were associated with EOL study enrollment. Clinicians, researchers, and policy developers should work together to explore approaches to ensure broader trial accessibility and equity of access so that diverse participants can participate in and benefit from research. The impacts of enrollment on the EOL experience should be studied further.

Table 2.1. Demographic characteristics of patient population, stratified by enrollment in early phase study

	Overall n=3125	Not Enrolled in Early Phase Trial n=2985	Enrolled in Early Phase Trial n=140	p-value*
Patient Characteristics				
Median Age at Death, (IQR)	8.84 [4.27, 13.96]	8.82 [4.22, 13.99]	9.05 [5.36, 13.41]	0.813
Sex, n (%)				0.454
Male	1723 (55.1)	1641 (55.0)	82 (58.6)	
Female	1402 (44.9)	1344 (45.0)	58 (41.4)	
Race, n (%)				0.449
White	1807 (57.8)	1725 (57.8)	82 (58.6)	
Non-white	598 (19.1)	572 (19.2)	26 (18.6)	
Mixed	108 (3.5)	100 (3.4)	8 (5.7)	
Other/not available	612 (19.6)	588 (19.7)	24 (17.1)	
Dwelling at Diagnosis, n (%)				0.586
Urban	2526 (80.8)	2414 (80.9)	112 (80.0)	
Rural	580 (18.6)	552 (18.5)	28 (20.0)	
Missing	19 (0.6)	19 (0.6)	0	
Income Quintile, n (%)				0.001
3-5 (Higher)	1856 (59.4)	1752 (58.7)	104 (74.3)	
1-2 (Lower)	1219 (39.0)	1184 (39.7)	35 (25.0)	
Missing	50 (1.6)	49 (1.6)	1 (0.7)	
Disease Characteristics				
Cancer Diagnosis at Time of Death, n (%)				0.019
CNS Tumor	1088 (34.8)	1024 (34.3)	64 (45.7)	
Solid Tumor	1141 (36.5)	1101 (36.9)	40 (28.6)	
Leukemia & Lymphoma	896 (28.7)	860 (28.8)	36 (25.7)	
Metastases at Time of Death, n (%)				0.107
Non-metastatic	1807 (57.8)	1714 (57.4)	93 (66.4)	
Metastatic	1157 (37.0)	1116 (37.4)	41 (29.3)	
Missing	161 (5.2)	155 (5.2)	6 (4.3)	
History of Relapse (before EOL Period), n (%)				0.543
No	2050 (65.6)	1962 (65.7)	88 (62.9)	
Yes	1075 (34.4)	1023 (34.3)	52 (37.1)	
Median Years from Diagnosis to Death, in Years, (IQR)	1.16 [0.56, 2.28]	1.17 [0.55, 2.29]	1.04 [0.75, 2.07]	0.603

Treatment-related Characteristics				
Previous Radiotherapy (before EOL Period), n (%)				<0.001
No	1621 (51.9)	1570 (52.6)	51 (36.4)	
Yes	1504 (48.1)	1415 (47.4)	89 (63.6)	
Previous Cellular Therapy (before EOL Period), n (%)				0.43
No	2473 (79.1)	2358 (79.0)	115 (82.1)	
Yes	652 (20.9)	627 (21.0)	25 (17.9)	
Previous Clinical Trial Enrollment (before EOL Period), n (%)				<0.001
No	2391 (76.5)	2350 (78.7)	41 (29.3)	
Yes	734 (23.5)	635 (21.3)	99 (70.7)	
Initial Treatment in a Major Early Phase Study Center				<0.001
No	1882 (60.2)	1821 (61.0)	61 (43.6)	
Yes	1242 (39.7)	1163 (39.0)	79 (56.4)	
Missing	1 (0.0)	1 (0.0)	0	

* p-values calculated using chi squared tests for categorical variables and Wilcoxon rank sum tests for continuous, non-normally distributed variables

Abbreviations: CNS – Central Nervous System; EOL – End of Life; IQR – interquartile range

Table 2.2. Univariate logistic regression describing relationship between predictor variables and enrollment in an early phase study

Characteristic	Number of Deaths n=3125	OR	95% CI	p-value*
Age at Death		1.00	0.97, 1.03	0.916
Sex				0.402
Male	1723	—	—	
Female	1402	0.86	0.61, 1.22	
Race				0.719
White	1807	—	—	
Non-White/Mixed	706	1.06	0.70, 1.59	
Not Available/ Other	612	0.86	0.53, 1.34	
Dwelling at First Diagnosis				0.683
Rural	580	—	—	
Urban	2526	0.91	0.61, 1.42	
Income Quintile				<0.001
3-5 (Higher)	1856	—	—	
1-2 (Lower)	1219	0.50	0.33, 0.73	
Last Cancer Diagnosis				0.021
CNS	1088	—	—	
Leukemia & Lymphoma	896	0.67	0.44, 1.01	
Solid Tumor	1141	0.58	0.39, 0.87	
Metastasis at Last Cancer Diagnosis				0.037
Non-Metastatic	1807	—	—	
Metastatic	1157	0.68	0.46, 0.98	
History of relapse before EOL				0.487
No	2050	—	—	
Yes	1075	1.13	0.79, 1.60	
Time from First Diagnosis to Death		0.99	0.90, 1.08	0.832
History of Cellular Therapy before EOL				0.362
No	2473	—	—	
Yes	652	0.82	0.51, 1.25	
History of Radiation before EOL				<0.001
No	1621	—	—	
Yes	1504	1.94	1.37, 2.77	
Number of Trial Enrollments before EOL		2.88	2.36, 3.51	<0.001
Initial Treatment in a Major Early Phase Study Center				<0.001
No	1882	—	—	
Yes	1242	2.03	1.44, 2.86	

*p-values under threshold for inclusion in multivariate modelling (0.25) are in bold

Abbreviations: CI – Confidence Interval; CNS – Central Nervous System; EOL – End of Life; OR – Odds Ratio

Table 2.3. Multivariate logistic regression describing relationship between predictor variables and enrollment in an early phase study

Characteristic	Number of Deaths n=3125	OR	95% CI	p-value*
Income Quintile				0.004
3-5 (Higher)	1757	—	—	
1-2 (Lower)	1161	0.56	0.37, 0.84	
Last Cancer Diagnosis				0.006
CNS Tumor	1016	—	—	
Leukemia & Lymphoma	817	0.54	0.33, 0.87	
Solid Tumor	1085	0.48	0.29, 0.79	
Metastasis at Last Cancer Diagnosis				0.223
Metastatic	1777	—	—	
Non-Metastatic	1141	0.76	0.49, 1.18	
History of Radiation before EOL				0.457
No	1477	—	—	
Yes	1441	1.16	0.78, 1.75	
Number of Trial Enrollments before EOL	2918	3.02	2.43, 3.77	<0.001
Initial Treatment in a Major Early Phase Study Center				0.008
No	1721	—	—	
Yes	1197	1.65	1.14, 2.40	

*p-values that are significant, i.e., <0.05 are in bold

Abbreviations: CI – Confidence Interval; CNS – Central Nervous System; EOL – End of Life; OR – Odds Ratio

Table 2.4. Description of the treatment plans that patients were enrolled on in the EOL Period

	Treatment plans for the 140 patients enrolled in Phase I/II studies Number of plans, n=142	
Conventional Chemotherapy, n (%)		
	No	34 (23.9)
	Yes	108 (76.1)
Targeted Agent, n (%)		
	No	93 (65.5)
	Yes	49 (34.5)
Immunomodulator, n (%)		
	No	121 (85.2)
	Yes	21 (14.8)
Anti-angiogenic Agent, n (%)		
	No	135 (95.1)
	Yes	7 (4.9)
Oral**, n (%)		
	No	52 (36.6)
	Yes	90 (63.4)
Intravenous, n (%)		
	No	58 (40.8)
	Yes	84 (59.2)
Intrathecal, n (%)		
	No	126 (88.7)
	Yes	16 (11.3)
Intramuscular, n (%)		
	No	131 (92.3)
	Yes	11 (7.7)
Only Oral Agents**, n (%)		
	No	84 (59.2)
	Yes	58 (40.8)
CART Therapy, n (%)		
	No	135* (95.7)
	Yes	*
131I-MIBG therapy, n (%)		
	No	142 (100)
	Yes	0
Pharmacokinetic or Biomarker Blood Tests, n (%)		
	No	47 (33.1)
	Yes	95 (66.9)
Study Completion		
	Terminated Early	125 (88.0)
	Completed as Planned	13 (9.2)
	Missing	4 (2.8)
Reasons for Non-Completion		
	Progression/Relapse	53 (42.4)
	Death	22 (17.6)

Physician Preference	*
Child/Family Preference	*
Toxicity	*
Other	*
Missing	43 (34.4)

* Values rounded/redacted to protect participant confidentiality (cell size<6)

** Oral indicates that the protocol included one or more agents given via the oral route, Oral only indicates that all agents in a protocol were given orally

Abbreviations: CART - chimeric antigen T-cell receptor therapy; 131I-MIBG - metaiodobenzylguanidine (MIBG) therapy

Table 2.5. Description of the EOL course of enrolled patients

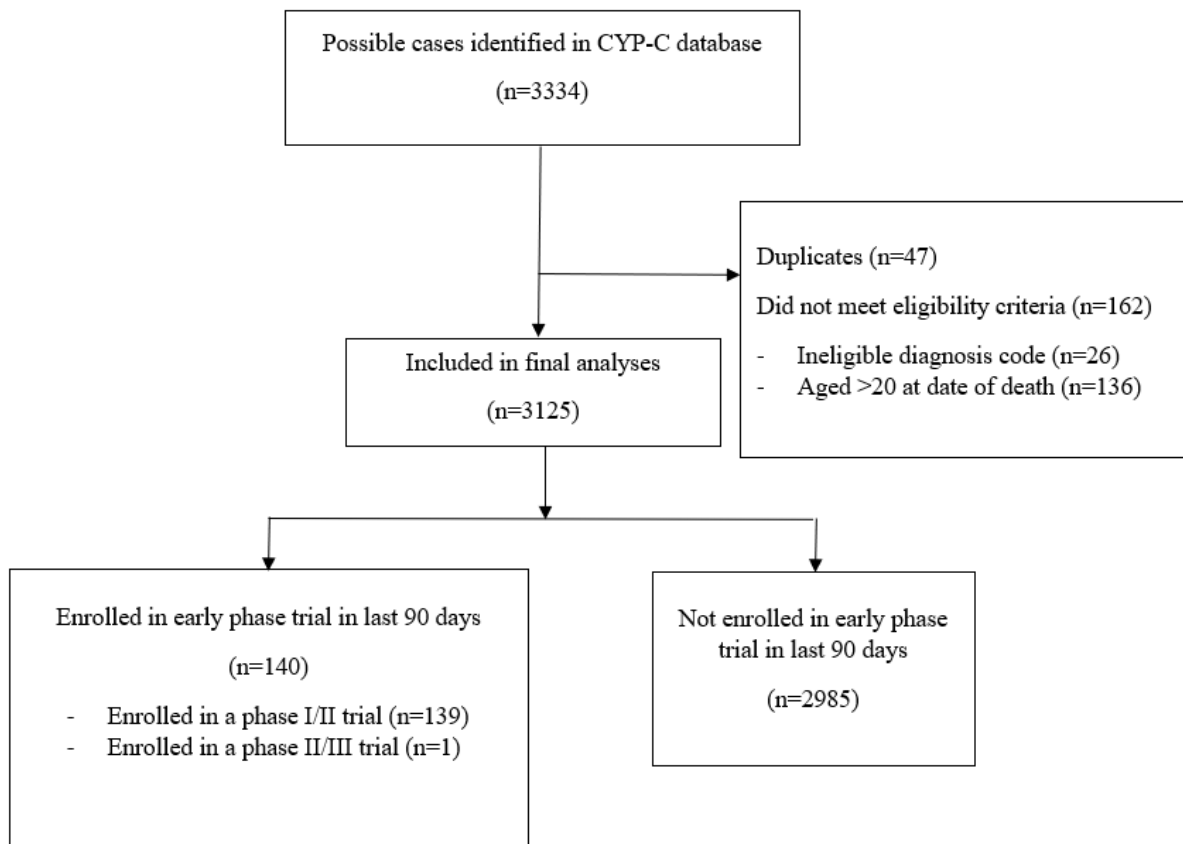
	Enrolled in Early Phase Trial n=140
Received one or more courses of radiotherapy during EOL period, n (%)	
No	115 (82.1)
Yes	25 (17.9)
Received HCT during EOL period, n (%)	
No	134* (95.7)
Yes	*
Experienced \geq grade 3 adverse event in EOL period, n (%)**	
No	65 (46.4)
Yes	19 (13.6)
Median days admitted to hospital in EOL period (IQR)**	9 [2, 45]

* Values rounded/redacted to protect participant confidentiality (cell size<6)

**Hospitalization and complications data available for 82 non-Ontario patients out of the total 140 patients who were enrolled in an early phase trial

Abbreviations: EOL – End of life, HCT – Hematopoietic cell transplant, IQR – interquartile range

Figure 2.1. Flow diagram of patient identification and selection



Chapter 3

End-of-Life Childhood Cancer Research: A Systematic Review

Reproduced with permission from Pediatrics. Hasan F, Widger K, Sung L, Wheaton L. End-of-Life Childhood Cancer Research: A Systematic Review. *Pediatrics*. 2021 Mar;147(3):e2020003780. doi: 10.1542/peds.2020-003780. PMID: 33597286.

3.1 Abstract

Context: Children with incurable cancer may participate in early phase clinical trials or palliative care research at the end of life (EOL). These studies create knowledge that can improve the care of future patients. *Objectives:* To describe the perspectives of stakeholders regarding research studies involving children with cancer at the EOL by conduct of a systematic review.

Data sources: OVID Medline, EMBASE, CINAHL, PsycINFO, Web of Science, Proquest (inception until August 2020). *Study selection:* We selected twenty-four papers, published in English that focused on perceptions or experiences of research participation for children with cancer at the EOL from the perspectives of children, parents and health professionals (HPs).

Data extraction: Two authors independently extracted data, assessed study quality and performed thematic analysis and synthesis.

Results: Eight themes were identified:(1) seeking control; (2) faith, hope and uncertainty; (3) being a good parent; (4) helping others; (5) barriers and facilitators; (6) information and understanding; (7) role of HPs in consent and beyond; and (8) involvement of the child in decision making. *Limitations:* Study designs were heterogeneous. Only one study focused on palliative care research. *Conclusions:* Some families participate in EOL research to gain control and sustain hope, despite uncertainty. Other families choose not to participate in research, instead prioritizing quality of life. Parents may perceive research participation as the role of a ‘good parent’ and hope to help future patients. HPs generally have positive views of EOL research but fear that parents lack understanding of the purpose of studies and likelihood of benefit. We identified barriers and facilitators to research participation and informed consent.

3.2 Introduction

Despite improvements in survival rates, around 20% of children with cancer still die of their disease or its treatment⁶⁷. Some of these children and their families are offered, and consider participating in, early phase (phase I or II) research studies towards the end of life (EOL)²¹. These studies usually test new chemotherapeutic agents^{6,7}. Objectives of these studies include to identify maximum tolerated drug doses and potentially to provide initial information on efficacy to inform future research⁴. Children with cancer may also be eligible to participate in palliative and EOL research studies. Delivering palliative care in pediatric oncology can be challenging due to the complexity of symptoms and the sensitivity of dealing with difficult decisions^{12,18,39,68-70}. However, there is a paucity of evidence available to guide practice, and a lack of research studies performed to address this evidence gap^{13,14,18-20}. Although participants may benefit from enrollment in both early phase and palliative care studies, the primary intention is to produce generalizable knowledge that will benefit future patients^{6,7}.

Concerns are often expressed regarding the vulnerability of children and families nearing the EOL, the burdens that research may place on them, and the ethics of research in this context^{26,28}. Research ethics boards may hesitate to approve any type of study involving these patients, and health professionals (HPs) may hesitate to suggest enrollment²⁷. With regard to early phase studies, further concerns have been expressed relating to therapeutic misconception: despite the purpose of these trials being to benefit future patients, patients may enroll believing that they are designed primarily to benefit current research participants^{8,9,71}.

While it is important to understand the views of stakeholders in pediatric oncology research at the EOL, including children, parents, and HPs, this area has been relatively under-explored. A number of reviews have been published on the subject of EOL decision making in pediatric oncology, but none discuss decisions relating to research enrollment in detail^{72,73}.

Studying the decision-making process around EOL research is important as it will allow HPs to understand how families make the challenging decision for their child to participate in research and guide HPs in counselling families around research enrollment. Furthermore, allowing HPs to

understand families' perspectives may help manage differences in opinions around research participation between medical teams and families. Researchers will benefit from understanding families' and HPs' experiences, which will assist them in designing studies that are acceptable to families and HPs, and inform the recruitment process.

In this review, we set out to answer the following research questions: *What are the perceptions and experiences of children with cancer, their parents and the HPs that treat them on the enrollment of children with cancer in phase I or other research studies at the EOL? How do the perceptions of these stakeholders compare with each other with regards to research enrollment?*

3.3 Methods

3.3.1 Information Sources and Database Searches

A protocol was developed *a priori*, following the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) and Preferred Reporting items for Systematic Reviews and Meta-Analyses statements (PRISMA)^{74,75}. A literature search was designed and conducted with the aid of a health librarian using Ovid Medline, Embase, CINAHL, PsycINFO, Web of Science and Proquest (inception to August 19th, 2020). The search strategy (Supplementary Table 3.1 – Appendix B) included subject headings and keywords for the following concepts: (1) children and adolescents, (2) cancer, (3) clinical trials, (4) and terms relating to perceptions, understanding and decision making.

3.3.2 Study Selection

Included studies focused on perceptions or experiences of research participation for children and adolescents with cancer at the EOL from the perspectives of pediatric patients with cancer (<21years), their parents/guardians or HPs involved in caring for this population. EOL research participation was defined as the enrollment in research studies by children whose cancer was no longer thought to be curable by standard treatments, within what was thought to be the last few months of life. This encompassed *any type of research* including palliative care and symptom management studies as well as studies of anticancer treatments. To be included, primary research

studies needed to *explicitly* discuss research enrollment and not just the broader topic of EOL decision making. Exclusion criteria were as follows: (1) not a fully published peer-reviewed study (conference proceeding or grey literature), (2) review articles or editorials, (3) not published in English language, (4) duplicate publications, (5) studies including adult patients where results relating to patients <21years could not be extracted separately, (6) studies including non-EOL research where results related to EOL research could not be extracted separately, (7) studies focused on EOL decision making in general without *explicitly* discussing decision making about EOL research. The search was supplemented by examining the bibliographies of included studies. Two authors (FH and LW) independently screened titles and abstracts to identify potentially eligible studies. Full text was retrieved for these studies and evaluated for eligibility by the same two reviewers who applied the eligibility criteria.

3.3.3 Data Extraction and Quality Assessment

Two investigators (FH and LW) independently extracted data and appraised studies. Studies were classified as qualitative or quantitative (survey-based or retrospective case series). Relevant criteria from three tools were used for study quality appraisal: the Consolidated Criteria for the Reporting of Qualitative Evidence (COREQ) checklist for qualitative studies⁷⁶; the BMJ Critical Appraisal Checklist for a Questionnaire Study⁷⁷ for survey-based studies, and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series⁷⁸. No study was excluded due to quality.

3.3.4 Synthesis

Two investigators (FH and LW) inductively coded the text included in the results section of each (qualitative or quantitative) paper, line by line. Thematic synthesis was performed by first grouping codes into descriptive then analytic themes, with translation of themes across studies⁷⁹. The authors independently performed initial analyses, then developed the synthesis together through iterative discussion.

Any disagreements in study selection, data extraction, quality assessment and synthesis were resolved by discussion. Conflicts in study selection and other review procedures were resolved through discussion with a third reviewer (KW).

3.4 Results

A total of 15203 papers were identified, of which 24 were included for analysis (Fig. 1). One of the 24 included papers was categorized as a palliative care research study, while the remaining 23 studies were categorized as phase I anti-cancer treatment studies. Eleven papers used qualitative methods, while thirteen used quantitative methods, eleven of which were surveys and two of which were retrospective case series (Tables 3.1, 3.2 and 3.3). These 24 studies included 1787 participants (162 patients aged 6-21years old, 904 parents and 721 HPs). One study included 2 surveys without reporting the number and type of individuals participating in the second survey¹⁹. Similarly, a retrospective case series reported the perspectives of HPs without stating how many HPs' views were described⁵⁰.

3.4.1 Quality Assessment

The eleven included qualitative studies met between 10 and 22 of the 32 items on the COREQ checklist (Supplementary Table 3.2)⁷⁶. Four of the survey-based studies included some qualitative findings thus 26 quality criteria in the BMJ checklist were relevant and 11 to 14 were met (Supplementary Table 3.3)⁷⁷. The remaining 7 survey-based studies were purely quantitative and met 7 to 21 of 24 relevant criteria. Survey instruments were only available for review from 4 studies^{40,41,80,81}. All the studies used a new survey, a pre-existing unvalidated survey, or adapted a previously validated survey without re-validation. The two case series met 2 to 7 out of 7 quality criteria in the JBI checklist⁷⁸.

3.4.2 Synthesis

Eight themes were identified (Fig. 3.2 and Table 3.4).

3.4.2.1 Seeking Control

Wanting Choices

Many parents and patients considering phase I studies actively searched for cancer treatment options but believed that these options were increasingly limited (or non-existent)^{37-39,82-85}. They had exhausted any curative treatments and now perceived the decision to be ‘phase I or nothing’^{37-39,85}. In contrast, HPs did not espouse the idea that families participated due to a lack of choice, and talked of presenting families with options including palliative care^{39,42,80,81,84,86}. Despite this, many families did not feel that palliative care alone was a viable alternative^{37,85}.

Trying Anything

Parents and patients participated in phase I trials to access treatment with even a remote chance of keeping the child alive^{38,39,86,87}. Regardless of the final outcome, they needed to know they hadn’t ‘given up’^{38,39,83,87}. HPs were conscious of families’ desire to ‘try anything’^{37,39,41,42,80,81,87,88}, perceiving it to be a significant barrier to informed consent⁸¹.

Awareness of Poor Prognosis

Many parents and patients alluded to expected poor outcomes^{37-39,83,84,86}. Some talked of miracles, while recognizing that the chances of cure were low³⁸. Other parents only questioned their research participation after they saw their child decline or fail to improve on study³⁸.

3.4.2.2 Faith, Hope and Uncertainty

Hope

For many patients and parents, the desire to ‘try anything’ was motivated by optimism; predominantly hope for a cure^{37-39,82,83,86,87,89,90}. Others knew that currently available trials were

unlikely to offer cure, but participated in the hope that their child might survive until a cure became available^{38,82,91}. For a smaller number of parents and children across multiple studies, participation was motivated by other desires like hopes for prolonging life^{37-39,82,83,87,92} or improving symptoms^{38,39}.

HPs commonly described symptom improvement as a reason to enroll children in trials^{40,42,86,88}, but did not discuss longer life or cure as potential benefits⁸¹. However, HPs were aware of families' desire to maintain hope for a cure through research participation^{39-42,80,81,86,88}. A minor theme expressed by HPs across several studies was the ethical concern that offering families phase I trials may encourage 'false' or 'unrealistic' hope^{40-42,88,93}. These HPs identified difficulties in ensuring realistic expectations, particularly when obtaining consent for research participation^{80,81}. Some HPs talked of encouraging families to focus on more achievable goals than cure, for example, symptom relief or a peaceful death⁸⁶.

Uncertainty

Despite hoping to benefit from trial participation, many parents and children expressed concern as to whether participation was ultimately the right decision for them and about the possible outcomes^{37,38,82,91}.

Faith

A small number of parents and children, but not HPs, discussed the role of religion and spirituality in guiding decisions and sustaining hope^{37-39,82,89,90}.

3.4.2.3 Being a Good Parent

Fulfilling a 'Good Parent' Role

This theme was discussed only by parents. According to some participants, a ‘good parent’ was an expert on their child: extensively researching potential treatments; protecting and advocating for their child, while considering the opinions of others, including their child, family and HPs^{37-39,83,86}. Many parents perceived the ongoing quest for cure to be a fundamental aspect of this role, only considering noncurative options once cure seemed impossible^{38,84}.

Acting in the Child's Best Interest

Again, this concept was only described by parents. Parents talked of ‘doing right’ by their child: considering the facts and making decisions that put the child first^{37,39,83,87}. In particular, while many parents had altruistic goals for research participation, they prioritized their child’s wellbeing^{39,83,87}.

3.4.2.4 Helping Others

Altruism

Many children and parents hoped to help others through research participation^{19,36-39,82,83,86,87,89,90,92,94}. Some families stated expressly that it was acceptable for HPs to mention possible benefits for other families, and participated with this intention⁹². Some wished to prevent others from experiencing the suffering they had lived through⁸⁷. They valued research and sometimes hoped to help HPs out of gratitude^{19,89,90,94}. In contrast, HPs believed that families made decisions in their own child’s interest, with benevolence playing a minor role^{41,42}. Many HPs avoided discussing this topic with families altogether^{80,81}.

Legacy

A minority of parents talked about helping others through research participation as a way of finding meaning in their experience, particularly after their child’s death^{37-39,83}. In contrast, HPs rarely discussed meaning or considered it to be a benefit of participation⁴².

3.4.2.5 Barriers and Facilitators

Access to Trials

Parents discussed time pressures inherent in phase I enrollment: limited spaces in trials necessitated quick decisions, constraining their ability to consider the options^{38,86}. Other fears included their child's possible deterioration before receiving trial medications or failure to meet study requirements, losing their place^{37,38,86}. Some parents coped by making one or more contingency plans³⁸. HPs were aware of this parental urgency⁸⁶.

Burden of Participation

All three types of participants considered the possible effects of studies on quality of life (QOL)^{19,38-40,42,50,80,82,83,86-92,94}. Some chose research participation hoping to improve QOL^{38,39,82,84}, while others tolerated possible temporary decreased QOL to allow study involvement^{39,82}. Still others chose not to participate, fearing reduced QOL due to side effects, invasive procedures or psychological suffering^{39,50,83,89-92,94}. Families considered their child's current state of health and ability to tolerate further treatment, sometimes deciding against study enrollment for unwell or symptomatic children^{19,38,39,95}. HPs perceived that potential toxicity was a common reason for families not to participate^{40,68}.

Familiarity and Convenience

Parents, and to a lesser extent, children and HPs, referred to practical facilitators of enrollment^{36,38,83,88}. Parents felt comfortable with their child receiving treatments they had previously been given in hospitals known to them^{38,83}. Transferring care to another medical team to facilitate research participation meant having to retell their 'story', establish new relationships, and deal with possible miscommunication between teams¹⁹. Time spent in hospital^{19,39,92,94}, particularly at short notice, travelling to receive treatment^{36,38,94}, and interruptions to family life⁹⁴ were other barriers to enrollment.

3.4.2.6 Information and Understanding

Practicalities of Consent

Parents and children appreciated receiving study information prior to discussions with HPs³⁶. They valued the opportunity for multiple meetings^{36,80,81,86} in comfortable locations³⁶ and having time for decision making^{36,39,86}. Families welcomed having easy access to HPs when questions arose³⁶.

Honest, Clear Communication

Parents and children described consent as involving large amounts of complex oral and written information^{36,86}. They preferred succinct, forthright language, tailored to their needs in quantity and complexity^{36,86}. Families appreciated receiving multiple forms of information (e.g. verbal, pictorial and written) to suit different learning styles³⁶. HPs agreed that consent processes, specifically paperwork, were lengthy and complex, in part due to regulatory requirements^{40,41,81,88}.

Specific Information Needs

Families appreciated that HPs discussed certain issues during the consent process : summarizing the child's previous treatment and current status^{36,84}, clarifying the options^{36,38}, providing details about individual trials^{36,82,84}, particularly about how other participants had fared^{36,38,39,82}. After consenting to participate, families desired regular, timely trial updates³⁶.

Participant Understanding

HPs believed that parents grasped basic aspects of phase I studies such as confidentiality, the right to withdraw, potential toxicity and alternative options⁸¹. However, they perceived that parents misunderstood complex concepts like dose escalation^{80,81}. Many HPs believed that families overestimated the likelihood of their child benefiting from participation^{40,88}, and failed to comprehend the goals of phase I studies^{41,81,88}. Consistent with this belief, in one study, adolescents' participating in phase I research claimed to understand study information, but

overestimated their chances of benefitting from participation⁸². In another study, parents showed poor understanding of risks, benefits and alternative options⁸⁵.

HP Beliefs and Understanding

In general HPs were aware of the goals of studies^{40-42,88}, but HPs working in different settings held different perspectives about phase I trials. Nurses were less likely than physicians to accurately perceive study goals and the probability of benefit or toxicity^{41,88}. HPs working in phase I consortium centers were more confident than those working outside these centers that trials benefited participants without causing ‘false’ hope⁴⁰. British oncologists expressed greater ethical concerns regarding phase I trials than US oncologists⁴².

3.4.2.7 Role of HPs in Consent and Beyond

Trust, Support, Reassurance and Guidance

Many families looked to HPs^{39,84} for advice that was consistent with their values^{36,38,86}. Often parents sought validation of their choices for fear of making ‘wrong decisions’^{38,39}. Many parents who chose experimental therapy, hoping for a cure, expected the backing of their HPs^{38,39,83}. Regardless of their choice, parents sought assurances that their child would receive the same standard of ongoing care^{39,83,84}. Some parents stated that HPs had previously provided treatment recommendations, and wanted advice, but stated that HPs felt parents should make choices in this situation^{36,38,86}. HPs referred to families’ needs for general multidisciplinary care, but despite parents’ desire for direction, preferred to avoid making specific recommendations^{40,42,81}. Some parents and HPs described physicians as holding simultaneous roles as clinicians and researchers^{37,93}. Both groups were aware of a potential role conflict, but parents hoped that HPs would prioritize their child despite their own research interests³⁷.

Training to Gain Informed Consent

Most HPs had only received informal instruction on taking informed consent for research participation, generally by observing senior colleagues^{80,81}. Many HPs believed that formal education would be beneficial^{80,81}.

Impact on HPs

HPs generally had positive perceptions of phase I research, believing that it was appropriate to respect family preferences to participate^{40,42,88}. A minority described ethical concerns, including the lack of benefit for participants, families' unrealistic expectations and misunderstanding of the purpose of studies^{42,88}. Few HPs described experiencing moral distress secondary to patients' involvement in phase I studies⁸⁸. Any impact of the tension HPs felt between clinical and research roles was rarely discussed³⁷.

3.4.2.8 Involvement of the Child in Decision Making

The child's role in the research consent process was a common theme. Parents and HPs talked of graded participation^{37,81,85,90}, with parents making choices on behalf of the youngest children^{37,81,85,90,92}, considering older children's preferences^{19,37,39,40,83-85,87}, and allowing the oldest children to choose for themselves^{41,82,85,88,92}. Many HPs suggested that although children could decide, often it was parents who did decide^{80,81}, or that children deferred to parental preferences⁸⁸. Decision making conflict was infrequently discussed^{89,92}, although parents in one study were more willing to accept their child's request to participate in research against parental wishes, than their refusal⁹².

3.5 Discussion

This review brings together patient, parent and HP perspectives on the topic of EOL research in pediatric oncology, with the intention of providing clinically relevant guidance to these groups.

Parents of children with incurable cancer and the HPs that treat them may find it helpful to discuss how other families make decisions about EOL research. We found that many parents sought a sense of control at the EOL by making choices, but experienced a somewhat contradictory position as the choices available to them increasingly diminished. Despite sometimes being presented with several choices, many parents only considered options that were associated with a chance of cure, however small. The implication is that, for many parents, palliative care without anticancer treatment was not a worthwhile choice.

Families making decisions about EOL research may also benefit from hearing of other families in our review who considered the practical inconveniences of research and potential interference in QOL and chose not to participate.

At times, differences of opinion arise in clinical practice as to whether research participation is in the interest of a particular child. We sought to identify differences in views of EOL research between children, parents and HPs, since understanding divergent perspectives may help HPs to manage conflict. One area of difference was perceptions of hope. Hope for a cure was commonly cited by families searching for any available treatment option. However, other hopes were also described and valued, such as hope for symptom relief. These findings echoed the results of other studies showing the importance of hope in promoting resilience for families of children with cancer⁹⁶⁻⁹⁹. In contrast, a small proportion of HPs in our review were concerned about familial hope. These HPs feared that consent could never be truly informed when participants were so determined to access treatment. Fewer HPs worried that hope could be ‘false’ and that families may be acting under therapeutic misconception^{8,29}.

These differences in families’ and HPs’ conceptions of hope are reflected in the broader literature¹⁰⁰⁻¹⁰². Whereas families may experience different types of hope, HPs typically focus on a limited vision of hope, such as hope for a cure^{100,101}. Where a cure is unlikely, HPs may worry that hopeful families are unrealistic and will pursue aggressive treatments at the EOL leading to

children suffering^{96,100-103}. It may help HPs to understand that for many parents, hope and the ongoing trial of new treatments was a key aspect of being a ‘good’ parent. This is consistent with related studies, notably Bluebond-Langer’s ethnography where parents felt driven to pursue further treatment, up until days before their child’s death^{96,97,104}. Similarly, the study by Tomlinson *et al* where parents of children with incurable cancer were more willing than HPs to accept chemotherapy for children at the EOL, even if treatment compromised QOL^{96,97}. Although there is some literature that demonstrates an association between hope, delayed prognostic understanding and aggressive EOL care, the findings of our and other studies suggest that parents can simultaneously be hopeful but also understand the prognosis^{101,102}.

We also identified differences in the ways that families and HPs approached altruism and legacy. While prioritizing their child’s interests, families found meaning and legacy in altruism. This is consistent with previous studies in adult and pediatric oncology⁴⁹. In contrast, we found that HPs were reluctant to discuss altruistic motivations for research participation, despite the primary intent of research studies to benefit future patients¹⁰⁵. Similarly, HPs avoided guiding parental decision making, although many parents desired guidance and support. It may be that HPs hesitate to influence parents or to discuss altruism for fear of coercion^{106,107}. However, the nature of phase I research means that discussions about altruism could be considered to be a critical aspect of informed consent and may help to avoid therapeutic misconception^{107,108}.

Lastly, we explored the perceptions of families and HPs regarding EOL research, so that researchers may use this information to guide study processes and design. Children, parents and HPs all found informed consent processes for phase I trials to be challenging, due to the requirement to transmit large amounts of complex information, often in short periods of time. Unsurprisingly, this was associated with a perceived lack of research participant understanding. These findings are supported by the broader literature on understanding in participants across adult and pediatric research¹⁰⁹⁻¹¹². We identified several possible improvements to the informed consent process, including the need for formal training of HPs in taking research consent¹¹¹. More research is needed on the child’s role in the consent process.

While we hoped to provide guidance that was grounded in child and adolescent perspectives of EOL research, it is important to note that the majority of participants in the included studies were

parents and HPs. Therefore, the perspectives of patients were under-represented. It may be that researchers hesitated to approach young people about a potentially sensitive topic. However, our findings indicate that children and adolescents played an increasing role in decision making with age and that many were willing to discuss their perspectives in studies included in this review. We would suggest that future research should investigate these perspectives further.

3.5.1 Strengths

A particular strength of this review is the inclusion of data from a broad range of perspectives, permitting comparison of the views of a range of stakeholders, and identifying areas for practice improvement.

3.5.2 Limitations

Despite conduct of a broad and systematic search, we only identified one study evaluating palliative care research. This may be due to a lack of both palliative care research and studies examining stakeholder perceptions of it. Our findings therefore relate primarily to phase I studies. Although many HPs were included, this was usually in survey-based studies, limiting the depth to which their opinions were explored. While several included studies used qualitative methods, they usually provided only ‘thin’ descriptions and limited data^{113,114}. The inclusion of heterogeneous data presented a challenge for synthesis.

3.5.3 Conclusions

Children with cancer, their parents and the HPs that treat them hold a broad range of perspectives regarding EOL research participation. Considering these perspectives and how they differ can help guide clinical and research practice. More research is needed to understand how these stakeholders, particularly the children themselves, view palliative care and other EOL research studies.

Table 3.1. Description of Included Qualitative Studies

Study, setting	Methodology	Qualitative Data Collection Method	Data Analysis Method	Participants			Research Topic
				Type (N)	M:F	Mean Age (y, range)	
Baker 2013³⁶, US	Qualitative	Secondary analysis of semi-structured interviews performed for a prospective descriptive study ¹⁰⁹	Semantic Content Analysis	Patients (20) Parents (57)	15:5 16:41	17.8, 14-21 41.1, 23-66	Informed consent for phase I pediatric oncology trials
Barrera 2005⁹¹, Canada	Qualitative	Individual semi-structured interviews	‘Qualitative Analyses’	Patients (3) Parents (9)	3:0 7:2	NS, 7-15 NS	Reasons for participation in phase I trials.
Beranger 2018⁸⁵	Qualitative/ Multiple Methods	Individual semi-structured interviews	Qualitative analysis using ‘validated code framework’ Logistic regression to identify correlates of understanding	Patients (37) Parents (119)	19:18 NS	*13.2, 11-15 NS	Understanding of and decision making relating to phase I research
Crane 2019³⁷, US	Qualitative (phenomenology)	Individual unstructured interviews	Adapted phenomenological analysis, as per Colaizzi ¹¹⁵	Parents (12)	10:2	NS	Parents’ experience of their child’s participation in phase I research
Deatrick 2002³⁸, US	Qualitative	Secondary analysis of interview data collected for a prospective descriptive study ⁶⁸	‘Qualitative Analyses’	Parents (21)	19:2	NS	Parents’ perceptions of their child’s participation in phase I research
Schröder Håkansson 2019⁹³, Sweden	Qualitative (grounded theory)	Individual unstructured interviews	Grounded theory, constant comparison	HPs (12)	2:12	NS	HPs’ experiences of informed consent process for oncology research, including phase I
Hinds 1997⁸⁴, US	Qualitative/ Multiple Methods	Semi-structured interviews and questionnaire	Content Analysis, Logistic regression to relate questionnaire data to qualitative data	Parents (39) HPs (21)	18:19 NS	NS NS	Treatment decisions faced by parents of children with cancer, including phase I participation, and factors influencing decision making

Hinds 2005³⁹, Australia & US	Qualitative	Semi-structured interviews	Semantic Content Analysis	Patients (20) Parents (19) HPs (14)	6:14 6:13 12:2	17.3, 10-21 NS NS	End-of-life care preferences of children with cancer, parents, HPs, including phase I participation
Johnson 2015⁸⁶, US	Qualitative	Parent advisory group discussion of data from previous studies ^{36,81,82}	NS	Parents (8)	1:7	42.3, NS	Informed consent process for phase I pediatric oncology trials
Maurer 2010⁸³, US	Qualitative	Secondary analysis of semi-structured interviews performed for a prospective descriptive study ¹¹⁶	Semantic Content Analysis	Parents (62)	NS	38.2, NS	Rationale for end-of-life decision making including phase I participation
Miller 2013⁸², US	Qualitative	Semi-structured interviews	NS	Patients (20)	15:5	17.8, 14-21	Adolescent perspectives on their understanding and decision making regarding phase I trials

Unless otherwise stated, no qualitative methodology was provided beyond ‘qualitative’ or ‘descriptive’. ‘N’ is the number of participants. ‘M:F’ indicates the ratio of male to female participants. Age is indicated in years. ‘NS’: Not stated.

*Median

Table 3.2. Description of Included Survey-Based Studies

Study, setting	Participants			Distribution Method	Research Topic
	Type (n) %	M:F	Mean Age (y, range)		
Barnes 2014⁴¹, US	MDs (94), 25 Nurses (122), 44	52:42 1:121	45.6, NS 40.7, NS	e-mail + web based survey + follow up reminder	Comparison of physicians' and nurses' working in pediatric oncology centers of phase I studies
Berg 2010⁹⁴, US	Patients (12), NS Parents (38), NS	NS	NS	NS	Attitudes of participants in phase I trials towards optional pharmacokinetic studies
Chang 2008⁸⁸, Canada	Nurses (43), 45	NS	NS	NS	Nurses' perceptions of phase I studies
Dussel 2015¹⁹, US	Survey 1: *65 Patients (7) Parents (87) Survey 2: **(46), 45	NS	NS	Survey 1: Administered in hospital OR mailed Survey 2: NS	Survey 1: Reasons for enrollment (or not) in an oncology palliative care randomized controlled trial. Survey 2: Reasons for ongoing participation in the same
Estlin 2000⁴², UK & US	MDs (131), 26	NS	NS	Mailed + reminder	Comparison of perspectives of UK/US pediatric oncologists regarding phase I studies
Gilliam 2013⁴⁰, US	MDs (94), 2, 5	NS	NS	e-mail + web based survey	Comparison of perspectives of oncologists in phase I participating institutions with those of oncologists in non-participating institutions regarding phase I studies
Kamps 1987⁹², Netherlands	Parents (168), 82	NS	NS	Permission requested to send survey (by phone call from MD or letter to be returned) + survey mailed if permission given	Perspectives of parents of childhood cancer survivors on the involvement of children in decisions about phase I/II study participation
Mack 2008⁹⁵, US	Parents (141), 64	24:117	***43.4, NS	Interviews by telephone	Perspectives of bereaved parents on cancer directed treatment for children with incurable cancer
Robertson 2018⁸⁰, Australia & New Zealand	MDs (44), NS Nurses (24), NS Other HPs (19), NS	All participants (n=69): 25:44	All participants (n=58): 43.8, 28-74	e-mail + web based survey OR handed out at a conference (NS how paper questionnaires were returned)	Perspectives of HPs working in pediatric oncology regarding phase I studies

Van Der Geest 2016⁸⁷, Netherlands	Parents (24), 35	10:14	46, 25-53	NS	Rationale for participation in oncology studies at the end of life and whether this was perceived to be a burden. Survey part of a larger study examining parental perspectives of pediatric palliative care ¹¹⁷
Yap 2010⁸¹, US	MDs (103), 71	51:52	42, NS	NS	Pediatric oncologists' opinions about the consent process for phase I studies. Part of a larger study examining consent for phase I studies ¹⁰⁹ .

‘N’ is the number of participants, ‘%’ is the response rate. M:F indicates the ratio of male to female participants. Age is indicated in years. ‘NS’: Not stated.

* Overall response rate, **Participant type not stated, ***Median

Table 3.3. Description of Included Retrospective Case Series

Study, setting	Participants			Research Topic
	Type (n)	M:F	Mean Age (y, range)	
Nitschke 1977 & 1982^{89,90}, US	Patients (43)	NS	NS, 6-20	Children’s reasons for their decision to participate or not in phase II studies for end stage cancer
Surun 2017⁵⁰, France	*Parents (100) HPs (NS)	NS	NS	Reasons for HPs’ decision not to offer or parents’ refusal to accept phase I study enrollment for children with progressive cancer

‘N’ is the number of participants, ‘%’ is the response rate. M:F indicates the ratio of male to female participants. Age is indicated in years. ‘NS’: Not stated.

*The charts of 100 patients were reviewed and perspectives of their parents, as documented by HPs in the charts, are reflected in the results. The exact number of parents whose children’s care are reflected is not stated in the publication.

Table 3.4. Illustrative Quotations

Theme and Participants	Source Text	Studies
Seeking Control		
<p>Wanting Choices C, P, H</p>	<p>“Because it’s a different opportunity—it’s a different treatment and I’ve pretty much exhausted most other treatments. . .” (Child)⁸²</p> <p><i>“Thirteen of the parents said that they did not have any choice in their situation. They knew that they signed a consent form, but, they didn’t think of it as a decision. These parents described “choice” in terms of the promise of potentially “curative” treatment, not in terms of providing comfort or palliation. ‘There wasn’t really a choice in my mind because if I chose to not do anything then I would have been choosing to let her go and I’m not ready for that.’” (Parent)³⁸</i></p> <p>“Nobody ever really counseled us on that. I also had this stigma about hospice services because I thought that was giving up, but it turns out [hospice services] was a very good decision.” (Parent)³⁷</p>	37-39,80,82-85
<p>Trying Anything C, P, H</p>	<p>“You have to try everything... keep fighting to keep her here with me. You have to do what you have to do.” (Parent)³⁸</p> <p><i>“The family continues to believe there is a chance for cure, and they expect the staff to support their desire for continued therapy.” (Parent)⁸³</i></p>	37-39,41,42,80,81,83,87,88
<p>Awareness of Poor Prognosis P</p>	<p>“For the parent, the enrollment decision is a ‘head versus heart’ struggle. The head knows that survival is unlikely, but the heart needs to believe there is hope.” (Parent)⁸⁶</p> <p><i>“with these studies...we aren’t even looking for the cancer to shrink; we’re just looking for it to stay at bay.” (Parent)³⁷</i></p>	37-39,83,84,86
Faith, Hope and Uncertainty		

<p>Hope C, P, H</p>	<p>“Hopefully, it will uh, make it longer. Before this I was only like given 6 months to live. And then now I think this will help.” (Child)⁸²</p> <p><i>“Some parents were hoping for a cure or a miracle, whereas others stated that this was not their expectation. Many admitted that they wanted a miracle, but that they might not get one.” (Parent)³⁸</i></p> <p>“I am...prolonging the inevitable until a cure comes along...I want her to be healed. I keep telling her to hold on...” (Parent)³⁹</p> <p><i>“No matter how you phrase it, families are going to perceive it as something that will potentially help their child. At least get some quality of life if not cure.” (HP)⁸⁶</i></p> <p>“The participants discussed whether an early/middle development study could hinder the child from receiving good palliative care or give the family unrealistic hopes of cure.” (HP)⁹³</p>	<p>37-42,80-83,86-93</p>
<p>Uncertainty C, P</p>	<p>“No one knows, . . . because it’s, again, undetermined how much benefit it will have.” (Child)⁸²</p> <p><i>“Nothing’s ever a given. Even in medicine that’s been proven...we knew that...everything was a ticking time bomb... We just knew that certain things would not work....it just seemed like [the PIT] was the one that offered the most hope. And, I don’t know if that was a tangible hope or not.” (Parent)³⁷</i></p>	<p>37,38,82,91</p>
<p>Faith C, P</p>	<p>“Half (n . 10) of participants indicated that faith was important to the decision, primarily because it gave them strength to make decisions.” (Child)⁸²</p> <p><i>“I don’t care what you want to call it, my belief had a lot to do with believing that there is something better out there for her.” (Parent)³⁹</i></p>	<p>37-39,82,89,90</p>
<p>Being a Good Parent</p>		
<p>Fulfilling a 'Good Parent' Role P</p>	<p>“Considering the facts, explanations, opinions, and preferences of experts and others (e.g., family members, ill child, and other bereaved parents) and then choosing the option most consonant with an internal definition of a caring, competent protector of their child.” (Parent)³⁹</p> <p><i>“On some level, every one of the 21 parents continued to view their role as parent and their human need to keep trying...” (Parent)³⁸</i></p>	<p>37-39,83,84,86</p>

	<p>“I knew all about this trial, I knew the details, everything on this trial before I walked into that consent. I had a stack every week of at least 5–10 different trials going on that I plowed through with my doctor....” (Parent)⁸⁶</p> <p><i>“It’s all on our shoulders.” (Parent)³⁷</i></p>	
<p>Acting in the Child's Best Interest</p> <p><i>P</i></p>	<p>“...every decision we have had to make, we considered what is best for her.” (Parent)⁸³</p>	37,39,83,87
<p>Helping Others</p>		
<p>Altruism</p> <p><i>C, P, H</i></p>	<p>“Doctors could lay out all the options if you’ve gone through the best and nothing’s really worked then emphasize how this could maybe help, and if not, it does help other people in years to come, hopefully.” (Child)³⁶</p> <p>“If it’s not going to help my child, if it’s going to save some other child from going through this or some other parent going through this then yes, I would do my child. I mean, it’s not hurting her any worse than what... the end result was going to be the same. It’s not hurting her to try.” (Parent)⁸⁶</p> <p><i>“...with medical benefit, altruism, and hope of cure being identified as reasons parents agree to enter their children onto a phase I study.” (HP)⁴²</i></p>	19,36-39,41,42,80-83,86-90,92,94
<p>Legacy</p> <p><i>P, H</i></p>	<p>“We feel that if he would die in a useful manner, it would kind of help cleanse us of the burden... give it a little bit of meaning... Whereas going home and dying on the bed to us is very meaningless and very frustrating, and just very damaging in every sense of the word... It’s family dealing with death in a very real [way]... At least we have made the effort... and enhanced some type of ongoing study... that would be my son’s legacy. (Parent)³⁸</p>	37,38,42,83
<p>Barriers and Facilitators</p>		
<p>Access to Trials</p> <p><i>P, H</i></p>	<p>“It was like whoever had the fastest finger is the one that got on the trial.” (Parent)⁸⁶</p> <p><i>“...timing was an important issue in their decision. They could get into a trial right now in their present treatment facility and if that trial failed, they could go to the other institution as backup.” (Parent)³⁸</i></p> <p>“...it’s important that...the people that are involved in this feels comfortable enough to openly include these</p>	37,38,86

	<p>things because if you are afraid that you are going to be kicked off the trial because you're on a medicine, you're not going to say something." (Parent)⁸⁶</p> <p><i>"Him being sick right now...we're trying not to give him any Tylenol or anything that could whack his body out'. This resulted from an overriding fear that additional medications could exacerbate toxicities...and cause the child's premature removal from the trial". (Parent)³⁷</i></p> <p>"Clinicians should address parents' fear that unless they make a rapid decision they risk losing their child's "spot" in a trial."(HP)⁸⁶</p>	
<p>Burden of Participation</p> <p>C, P, H</p>	<p>"I know I will go to Heaven. I want to be close to home." (Child)^{89,90}</p> <p><i>"This would have meant extra days in the hospital...injections at home...probably less time off between treatments. He might not get the time to recuperate in between." (Parent)³⁹</i></p> <p>"Disadvantages included...a sense of their lives revolving around the PIT". (Parent)³⁷</p> <p><i>"The patient factor 'avoiding adverse events,' the parent factor 'avoiding negative outcomes,' and the physician factor 'wanting to avoid harm' (68.4% to 78.6% of each group) reflected a common desire to prevent or reduce suffering or clinical deterioration." (Child, Parent, HP)³⁹</i></p>	<p>19,37- 40,42,50,80,82,83,86- 92,94</p>
<p>Familiarity and Convenience</p> <p>C, P, H</p>	<p>"They're being very good about giving me the option of doing stuff at our home hospital if needed versus having to travel up here, which I think is great." (Child)³⁶</p> <p><i>"The parent desires better and smoother transmittal of information between providers and between clinics; they do not like having to repeat things to multiple new people..." (Parent)⁸³</i></p> <p>".....the opportunity to participate in research and/or receive a treatment that was familiar to the parent made the option even more attractive..." (Parent)⁸³</p>	<p>19,36,38,39,83,88,92,94</p>
<p>Information and Understanding</p>		
<p>Practicalities of Consent</p> <p>C, P</p>	<p>"I definitely think-not that you or the doctor did anything wrong, but that I kind of felt that I wanted to just talk about it with my mom first, and I hadn't really got the chance to. (Child)³⁶</p>	<p>36,39,86</p>

	<p><i>“You know. . .a little video presentation or something talking about ‘getting ready for your phase I trial’ or something like that. And utilizing the internet.because people assimilate their information in all sorts of different ways and some people need diagrams and flowcharts and other people need explanations in words and things like that.” (Parent)³⁶</i></p>	
<p>Honest, Clear Communication</p> <p><i>C, P, H</i></p>	<p>“Individualize your approach: recognize families are different; provide information in a manner individualized to the needs/preferences of the particular child and family, including tailoring the amount of information they want.” (Child, Parent)⁸⁶</p> <p><i>“There is a lot of concepts going on, we’re talking about dose escalation, toxicity, and I realize that a lot of these that the physicians are melding it....it’s almost like teaching people to talk in paragraphs.” (Parent)⁸⁶</i></p> <p>“The informed consent documents are currently often 30 pages long. There is so much required language that points unique to that person are lost in the repetitive language. Consents could be simplified to improve patient understanding.” (HP)⁸⁶</p>	19,36,39-41,81,86,88
<p>Specific Information Needs</p> <p><i>C, P</i></p>	<p>“....reported the following staff behaviors as helpful: ‘explained everything to me/gave us written information’....., ‘answered my questions and gave me time to think’.....,‘told me about how other patients did’.....” (Child)³⁹</p> <p><i>“Provide more information about the specific phase I trial being considered, including detailed information regarding the mechanism, science, development, and side effects of the study drug.” (Child)(Parent)³⁶</i></p> <p>“Let us know about other kids on the trial: provide an update about enrollment and current patient status in advance of the decision to enroll on the trial.” (Parent)³⁶</p>	36,38,39,82,84
<p>Participant Understanding</p> <p><i>C, P, H</i></p>	<p>“When asked specifically whether most patients who participate in phase I trials receive medical benefit, 30% (n . 6) said ‘yes,’ 20% (n . 4) said ‘no,’ and 50% (n . 10) said ‘don’t know.’....When asked about their own chances of getting medical benefit, 13 (65%) participants answered ‘don’t know’ or did not provide a percentage, while seven provided percentages ranging from 5% to 100% (M . 55.71%; SD . 37.13). Participants rated the information that was given to them as easy to understand.” (Child)⁸²</p> <p><i>“The understanding by the parents of the purpose of the trial and of the potential individual benefits was poor...” (Parent)⁸⁵</i></p>	36,41,80-82,85,86,88

	<p>“...a large proportion of the nurses in this study (47%) felt that patients and families did not understand the goals of phase I clinical trials.” (HP)⁸⁸</p>	
<p>HP Beliefs and Understanding</p> <p><i>H</i></p>	<p>“Physicians were more likely to correctly identify the main goals of phase 1 studies including testing the safety, determining the maximum tolerated dose, and identifying the dose-limiting toxicity of an experimental drug. In addition to being less likely to correctly identify the main goals of phase 1 trials, nurses were more likely to incorrectly endorse goals including determining the efficacy of a drug for a specific disease and extending the life span of a patient. No providers endorsed curing patients as a goal of phase 1 therapy.” (HP)⁴¹</p>	40-42,88
<p>Role of HPs in Consent and Beyond</p>		
<p>Trust, Support, Reassurance and Guidance</p> <p><i>C, P, H</i></p>	<p>“So I asked for his opinion on whether I should do it or not, and he very carefully answered that it depends on what I value and whether I’m willing to take the risks and whether I’m looking for quality of life or looking for a treatment that works or how I view the situation, and that was good.” (Child)³⁶</p> <p><i>“Parents would like staff to accept them, to advocate and be there for their child, to provide comfort, and to treat the child the same as before the decision was made.” (Parent)⁸³</i></p> <p>“What made it so hard for me is that I’m not a doctor, and he was so well-educated. He usually guides me well with decisions, but he couldn’t tell me what to do here, and it made me feel so helpless... I wanted so much to have someone else tell me that I had made the right decision, but there isn’t anyone who can tell me that.” (Parent)³⁸</p> <p><i>“I am grateful. . .no one is giving up on us.” (Parent)⁸³</i></p> <p>“We were just prayerful that we were being pushed in this direction [to the PIT] for good reasons.” (Parent)³⁷</p> <p><i>“HCPs expressed the concept of being on both sides when they were conscious of their dual role. On the one hand, they were HCPs, building close relationships with parents and children, and on the other they were researchers/investigators, with responsibility for introducing and conducting clinical trials.” (HP)⁹³</i></p>	36-40,42,81,83,84,86,93
<p>Training to Take Consent</p> <p><i>H</i></p>	<p>“HCPs reported having received either informal training through the observation of mentors (52.3%, n = 45) or selfdirected learning (via conferences and literature) (37.2%, n = 32), with few having undergone a formal training programme (17.4%, n = 15).” (HP)⁸⁰</p>	80,81,86

<p>Impact on HPs</p> <p><i>H</i></p>	<p>“22 nurses (51%) in this study reported that they experienced ethical or moral conflict with the oncologists’ decision to offer phase I clinical trials to families and, to a lesser degree (15%), with the families’ decision to enroll in phase I clinical trials.” (HP)⁸⁸.</p> <p><i>“Physicians reported the following reasons for feeling okay about their part in a phase I decision: “consistent with my ethical standards” (HP)³⁹</i></p> <p>“...early and middle development studies (phase I/II) brought up more ethical challenges particularly whether participating in the trial was of benefit to the child.” (HP)⁹³</p>	<p>39,40,42,88,93</p>
<p>Involvement of the Child in Decision Making</p>		
<p>Involvement of the Child in Decision Making</p> <p><i>C, P, H</i></p>	<p>“Younger children were ‘too young to really have any conversations about what it [the cancer] meant’ and to ask tough questions, and did not remember any other way of living.” (Parent)³⁷</p> <p><i>“If I don’t take it, my family would support me, but they don’t want me to quit. Grandpa said he would worry himself to death if I don’t try it. My boyfriend wants me to take it for him. I don’t want to do it but for my family.” (Child)³⁹</i></p> <p>“The doctor gave us the facts and told us how serious this is, and we told our daughter. But the choice part has not been difficult for us. ...it’s never been a question for us because she has plans, and we are going to do everything we can to see that those plans are able to be made and, if not, then she knows and we know that we have done everything we can.” (Parent)³⁹</p>	<p>19,37,39-41,80-85,87,88,92</p>

‘C’, ‘P’ and ‘H’ indicate themes representing the perspectives of children, parents or health professionals respectively.

‘P1T’ refers to phase I trials

Figure 3.1. Flow of papers through the study

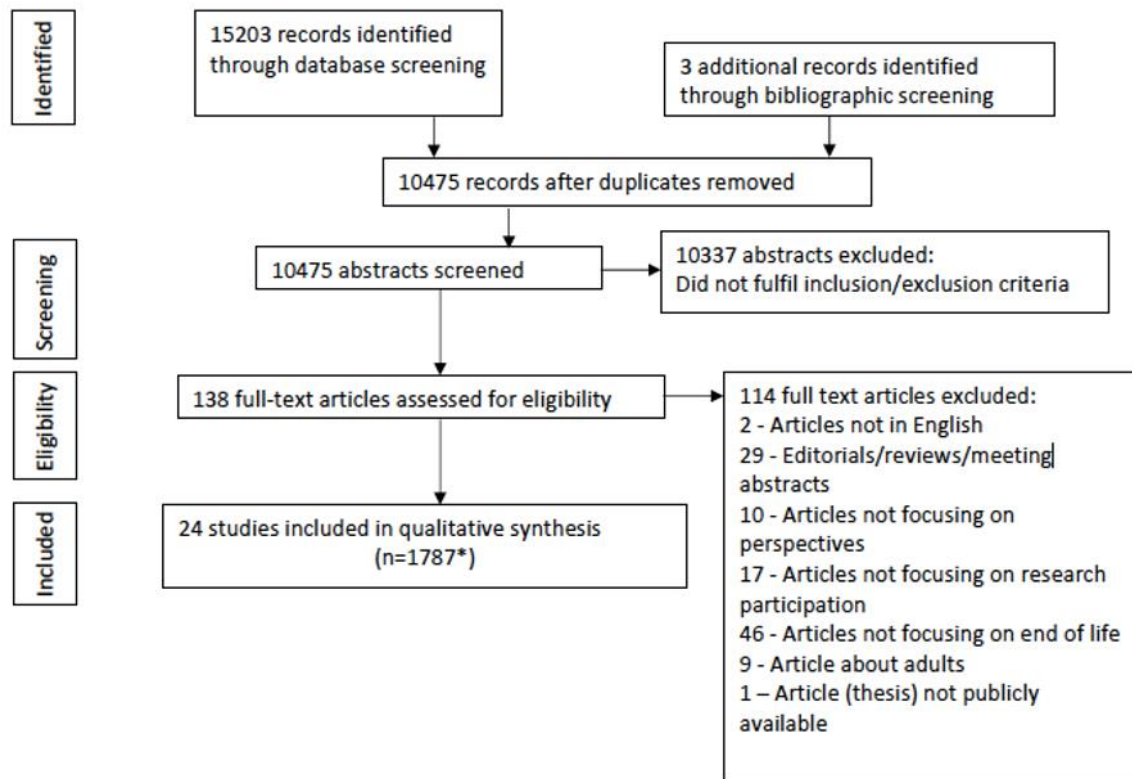
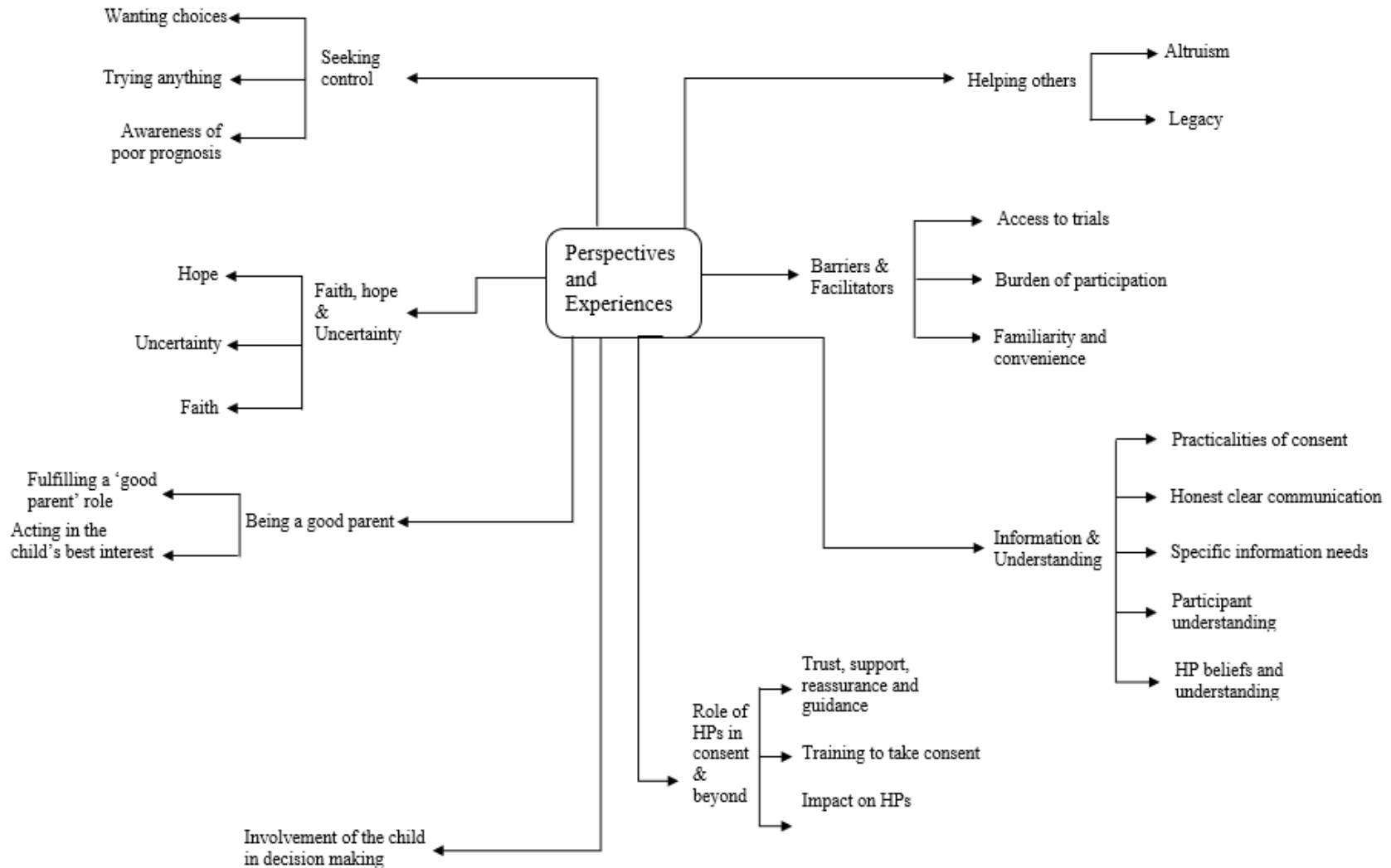


Figure 3.2. Thematic schema



Chapter 4

Ethical Issues and Interprofessional Tensions: Making Decisions about Research for Children with Cancer at the End of Life: A Qualitative Study

4.1 Abstract

Background and aims: Ethical concerns are commonly raised regarding the participation of children with cancer in research towards the end of life (EOL). Parents may misunderstand the purpose of early phase anticancer treatment trials, seeing them as last attempts of cure, rather than research, and children may suffer while receiving experimental therapies with low prospect of benefit. Palliative care studies exploring decision-making, care-delivery, communication and supportive therapies may be perceived to inconvenience or distress families. We sought to address current knowledge gaps, by exploring HPs perspectives about EOL research-related decision making. We aimed to describe how decisions are made, how interprofessional team members perceive and navigate ethical concerns and whether perspectives vary depending on the type of research.

Methods: We conducted individual semi-structured interviews with 35 HPs (oncology staff physicians, fellows, nurses, social workers, and palliative care physicians) at a Canadian pediatric oncology center. We sampled for maximum variability in HP roles and years of experience. Interviews were conducted, and data were analyzed by the lead author. Recruitment continued until the sample held adequate information power to address the topic, comparing perspectives across HP roles. We used interpretive description and reflexive thematic analysis as our qualitative methodological and data analytic approaches. Data were inductively coded, using a constant comparative process.

Findings: EOL research-related decision making occurred in an emotionally complex context that influenced communication and decisions that were made. HPs experienced dialectic tensions regarding research. For example, HPs felt conflicted by a tension to allow parents autonomy to enroll their children in early phase anticancer studies, versus wanting to protect children from the

consequences of parental decisions. Ethical tensions were experienced differently by HPs depending on their involvement in decision making and care: nurses particularly struggled as they were not included in decision making but administered study treatments and witnessed patient suffering. Benefits and burdens were seen to differ dependent on the type of research: concerns about the scientific merit and emotional harms of qualitative and experiential palliative care research influenced HPs to engage in gatekeeping.

Conclusions: Members of interprofessional teams experience challenging emotions and ethical tensions regarding EOL research participation for children with cancer. Targeted interventions are needed to support all members of the interprofessional teams in decision making and communication about decisions. HPs need training and support to manage the emotional demands of their work and understand emotional influences on decision making. Palliative care researchers should address the concerns of oncology HPs when planning, conducting and communicating about research studies involving this patient population, to encourage them to aid in recruitment.

4.2 Introduction

Children with cancer may participate in research towards the end of life (EOL). This research includes a spectrum of studies, from early phase (phase I/II) trials of anticancer therapies to palliative care research. Palliative care studies may be qualitative and experiential, or interventional, and may explore topics such as decision-making, communication, delivery of care and supportive therapies. EOL research contributes to ongoing improvements in the quality of care for children with cancer, creating generalizable knowledge that leads to improvements in survival, quality of life, and experiences of care^{4,18}.

However, concerns have been raised around EOL cancer research studies. Regarding early phase anticancer treatment trials, there are ethical concerns that patients and families may act under therapeutic misconception or misestimation, perceiving studies that are intended to generate knowledge as therapeutic options, designed for participants' benefit^{8,26}. Families may overestimate the chance of individual benefit, while risking exposure to harmful side effects^{9,118}.

Concerns relating to palliative care research have focused on potential distress and inconvenience that these studies may cause to children and families at the EOL^{30,32}.

Previous literature has explored the perspectives of health professionals (HPs) regarding early phase anticancer studies⁶¹. Although it is increasingly common that care is provided and decision making occurs in the context of interprofessional teams, the literature is largely restricted to the perspectives of oncologists, with limited inclusion of nurses and other HPs^{41,84,88,119}.

Furthermore, despite the complexity of EOL decision making about research, previous studies have primarily been survey-based and failed to describe in detail how complex decisions are made within teams, and how ethical and other concerns are viewed and managed. As identified by our systematic review, while previous studies explored perspectives on early phase anticancer studies, there is a dearth of evidence describing HP perspectives about palliative care research⁶¹.

We sought to address these gaps in the literature. Specifically, we hoped to understand how perspectives of EOL research vary across the interprofessional team, how decisions about research are made within teams, and how team members perceive and navigate ethical and other concerns. Finally, we sought to understand how perspectives varied depending on the type of research study (early phase anticancer treatment vs palliative care research).

4.3 Methods

4.3.1 Study Design

This study was informed by constructivist epistemology, with an assumption that knowledge and beliefs about the human world, including beliefs about EOL research-related decision making, are socially constructed.

We used interpretive description as our qualitative methodological approach^{120,121}. Interpretive description is designed to generate findings relevant and applicable to clinical practice. This approach acknowledges that individuals' experiences and perspectives are socially constructed and contextually dependent, but that they may also be shared. It seeks to understand the common aspects of human experience, whilst explaining the reasons why and ways in which individuals'

experiences differ. This approach is, therefore, consistent with a constructivist epistemology. Given that we sought to understand how and why HPs views varied, depending on their experiences and roles, this approach was consistent with our aims.

4.3.2 Use of Theory

Interpretive descriptions are typically inductive and do not use *a priori* theoretical frameworks, to avoid over-influence by previous work. However, some authors suggest that literature and theory can usefully inform study design¹²¹. We developed a conceptual framework of EOL research-related decision making using our systematic review findings and three conceptual models describing general aspects of EOL decision making(Appendix C.1)⁶¹. We mapped our review findings onto themes described by Kim *et al*, incorporating core concepts from the other two models^{93,122,123}. Kim's findings were used as the basis for our new conceptual framework since they describe decision making for an individual in the context of a family, making decisions with their HPs. The basic decision-making unit of Kim's framework is therefore relevant in pediatrics. Furthermore, as a meta-ethnography of other theories, models, and frameworks, Kim's framework has strong theoretical underpinnings. We incorporated theory into the design of our qualitative study, by using our framework to identify gaps in the literature. Our model also influenced the choice and framing of questions in the interview guide. However, we did not refer to this framework while analyzing data, allowing us to ground our findings in our data, consistent with our interpretive descriptive approach.

4.3.3 Setting and Participants

The study setting was a Canadian quaternary pediatric oncology center, which was chosen as the study site for several reasons. First, it treats a large heterogeneous population of children with cancer, with over 350 new diagnoses per year. Second, it is a research center with an active early phase anticancer treatment study program and several researchers who conduct palliative care research. Third, it provides a formal pediatric palliative care service.

Our sample included HPs in four interprofessional roles (oncology and palliative care staff physicians, oncology fellows, nurses and social workers) from the cancer program. We included interprofessional team members in these roles since they have the most intimate involvement in medical care and decision making. To participate, HPs needed at least one year's experience in

their current role and for oncology to be a major focus of their work, to ensure that they had enough exposure to EOL research-related decision-making.

4.3.4 Research Team

Members of the research team and their roles in the study are described in Supplementary Table 4.1 (Appendix C.2)

4.3.5 Procedures

4.3.5.1 Participant Recruitment

One author, (FH) used departmental contact lists to identify and email a study invitation to all individuals in eligible roles in the department. The stated purpose of the study was to describe factors that determine whether HPs offer children research (early phase anticancer treatment or palliative care studies) towards the EOL and the decision-making process. The invitation stated that individuals could participate regardless of their role in decision making. Two follow-up emails were sent. Individuals who expressed interest were eligible to be purposively selected based on the sampling strategy described below. If selected, they were invited to an individual interview. All interviews were led by the first author (FH) who started by explaining the study. The potential participant was given time to read the consent form and if they agreed, the interview continued.

4.3.5.2 Sampling Strategy

We used purposive, maximum variability sampling, with a goal to recruit a sample with variability in clinical roles and years' of experience¹²⁴. This decision was partly influenced by our systematic review that suggested differences in the perspectives between nurses and physicians. Participants' characteristics were known by the lead author (FH) through her work at the institution.

4.3.5.3 Data Collection

Individual interviews were conducted remotely using secure teleconferencing software or in-person depending on participants' preferences. At the start of each interview, participants completed a demographic questionnaire (Appendix C.3) followed by the interview questions. Interviews were video, or audio-recorded, per participant preference, and lasted between 60 and 75 minutes.

We used a semi-structured interview guide containing open-ended questions (Appendix C.4). The questions explored interviewees' perspectives and experiences around children's participation in EOL research, the decision-making process, and their role in it. As described above, the choice and framing of questions was influenced by our conceptual framework. However, in accordance with our inductive approach, we allowed participants to direct the conversation towards additional topics that they believed to be relevant to the overall objective of the research^{121,125}. Data collection and initial analysis were performed concurrently and iteratively, and changes were made to the interview guide, to permit exploration of themes as they were identified. As possible new themes were raised by participants, subsequent participants were asked to comment on these themes. The intention was to explore which themes were common across individuals and which were unique, and to understand factors that may influence perspectives, including professional role. For example, participants raised the issue of interprofessional tensions and hierarchy in decision making. By exploring this topic with subsequent participants, we were able to explore variation in perspectives. Similarly, although we sought to understand differences in perspectives about early phase research compared to palliative care studies, it was clear that participants had their own mental categorizations of types of research studies. By modifying the interview guide and using clarifying questions, we were able to explore perspectives despite varying conceptualizations of research.

Immediately following each interview, FH wrote analytic memos to document initial thoughts and reactions. In the week following each interview, a research assistant produced verbatim transcripts, including non-verbal communication such as body language (where interviews were video recorded) and pauses in speech. Identifying information was removed from transcripts. Transcripts were checked by FH while reviewing recordings, correcting transcription errors or uncertainties, which also served to enhance FH's familiarity with these interviews.

4.3.5.4 Data Analysis

We used reflexive thematic analysis as our analytical approach. This approach is consistent with our use of interpretive description, given that both reflexive thematic analysis and interpretive description seek to identify themes as “patterns of shared meaning” within data^{121,126}. Both approaches see findings as being co-created by the researcher and participants, resulting from the researcher’s reflective engagement with the data, rather than ‘emerging’ passively^{121,126}.

Before coding transcripts, FH read through several transcripts from participants in different healthcare roles. Having gained familiarity with the dataset and some similarities and differences in perspectives between participants in different roles, FH began coding oncologists’ transcripts (see below). We began with the oncologists given that our conceptual framework was largely based on their perspectives. Once these transcripts were coded and a thematic schema created, FH coded transcripts from other groups of participants, one group at a time, creating a *de novo* schema for each group, ensuring that new or different findings from each group were reflected in their schema.

Coding and generation of themes proceeded as follows: initially FH read each transcript several times, and subsequently made notes and underlined text containing ideas, stories, or themes that appeared to be important. After this, codes were generated inductively, after considering the data, and applied to the text. As coding continued, codes were amalgamated, deleted, and edited. As codes were created, they were inserted into the coding schema for each HP role, and grouped under major categories and thematic groups, that reflected possible relationships between codes. Constant comparison was used, coding schemas were continually revised as new transcripts were coded, and FH revisited previous transcripts (and schemas) iteratively as needed to compare coding. FH made reflexive notes during the analytic process, referring to these notes, and the memos written after each interview as data collection and analysis continued.

Data analysis was overseen by LG, an experienced health sciences qualitative researcher. Early in the analysis period, LG and FH met frequently to discuss and revise the initial coding, the development of themes, ongoing sampling, and modifications to the interview guide. During these meetings they discussed sections of coded text, asking whether alternative codes, themes, explanations, and relationships in the data made more sense, looking for contrary and confirming

data. As the analysis proceeded, FH and LG continued to discuss the ongoing development of themes and sampling. There were additional meetings with other members of the team where themes were presented and discussed.

We continued to recruit, interview participants, and analyze data until we considered the sample to hold adequate informational power. Information power is an approach to qualitative sample sizes, that asks whether a sample can provide sufficient information to meaningfully address and add to the body of knowledge on a given phenomenon^{127,128}. For this study, adequacy of information power also related to our ability to explore differences and similarities in perspectives across different professional groups. We considered this to be a more appropriate method of determining when to conclude interviewing than seeking theoretical saturation, given that did not seek to develop theory, which is the case when using grounded theory methodology¹²⁹.

We used NVivo 11, qualitative data analysis software, to manage and organize data.

In the manuscript, quotations were edited to increase readability without changing their meaning, e.g. by removing repeated words or disfluencies in speech such as “uh”. Clarifications added to quoted text were placed in square brackets. Given the small number of palliative care physicians in the department, we grouped quotations from oncologists and palliative care physicians, as being made by ‘staff physicians’ to protect confidentiality. Given the large number of fellows, their comments were not grouped with staff physicians. Where relevant, ‘I’ denotes the interviewer and ‘H’ the participant’s study identifier.

4.3.5.5 Reflexivity

The lead author, FH, who recruited and interviewed HPs, was a member of the department where participants worked. This gave rise to several reflexive considerations that we would like to acknowledge. First, FH is trained as an oncologist. Caring for patients who at times appeared to suffer whilst receiving experimental anticancer therapies close to EOL led her to develop a curiosity about how and why decisions were made regarding EOL research, and an interest in pediatric palliative care clinical practice, research and education. Becoming a parent gave her some insight into parental motivations to search for cures for their children. We acknowledge

that this influenced the questions that were explored in this study, and the lens that was applied in analysis. During the study, FH used reflective journaling and discussions with team members to interrogate decisions made and study findings, considering the influence of her own perspectives. Second, interviewees were aware of FH's palliative care interest. This interest would have influenced interviews, for example, during conversations about the value of palliative care research. Third, it should be noted that since FH was a trainee in this department, there were no power imbalances between her and the interviewees.

4.3.5.6 Ethical Approval

Ethical approval was granted by the Research Ethics Board at the Hospital for Sick Children.

4.4 Findings

Forty-five participants expressed interest in study participation. Eight participants were not chosen to participate while 37 were asked to schedule an interview. Two failed to schedule an interview and thus, a total of 35 participants were interviewed. Table 4.1 shows the characteristics of the participants.

In this section, we briefly describe our major themes and key findings. Our major themes were: i) risks and benefits of research participation at the EOL, ii) emotional influences on research-related decision making, iii) ethical tensions in decision making, iv) influence of professional role on experiences of decision making and v) impacts of providing emotionally and ethically challenging care.

To summarize our key findings, HPs universally believed that EOL research was valuable. However, many worried about research burdens for participants. HPs considered the benefits and burdens of early phase anticancer treatment studies to differ from those of qualitative or experiential palliative care studies. Interestingly, while all the interviewees acknowledged that early phase cancer treatment trials were research studies, it was clear that for many HPs, when making clinical decisions, they conceptualized these trials as the 'next therapeutic option'. For example, a staff physician discussed their approach to a child with relapsed disease:

Interviewer (I): You mentioned options for children as they relapse. What kind of options are you thinking about?

Participant: We go through a kind of hierarchy (hand gesture with one hand above their head, palm down) of evidence. We would start with whatever was standard of care, or if there was an open phase three trial. And then, increasingly, for many of the diseases there are standard of care relapse strategies that are not part of a clinical trial, but are our go-to options, and there may be multiple go-to options. And then, in terms of clinical trials, there may be phase two studiesand then, phase one at the bottom. (H13, Staff Physician)

As another staff physician indicated, patients and families similarly conceived of early phase studies as treatment rather than research, noting,

I think they see it as another treatment. (Staff Physician, H1)

In contrast, palliative care studies were seen solely as research and not clinical care, except for symptom management studies that included a treatment.

Participants described an emotionally complex context where decisions about research were made. Interrelationships existed between parental and HP emotions that affected communication and decision making. HPs perceived specific situations of research enrollment to be ethically concerning, describing the impacts of providing emotionally and ethically challenging care, and the influence of their role in the interprofessional team on those impacts.

In the subsequent sections and in Figure 4.1., we provide more detail to illustrate our major categories, themes, and subthemes. Table 4.2 provides illustrative quotations from participants.

4.4.1 Risks and Benefits of Research Participation at EOL

4.4.1.1 Importance of EOL Research

Universally, HPs perceived that EOL research was important, leading to scientific advancements in pediatric oncology, whether through improving survival or supportive and palliative care.

4.4.1.2 Burdens of EOL Research for Families

Despite the perceived importance of research, most HPs worried that it may put unreasonable demands on families. This worry was grounded in two beliefs. First, many interviewees felt that EOL research participation was potentially burdensome and inconvenient for the families involved, with the degree of burden and inconvenience depending on the study characteristics. Second, HPs perceived that these families were vulnerable and already burdened by advanced cancer, particularly as they approached EOL. Together, these two beliefs created hesitations about research studies, which some HPs felt ‘asked too much’ of families who were already coping with ‘too much’.

4.4.1.3 Weighing Risks against Benefits

Interviewees were easily able to identify the risks and benefits of research participation for children and families, described below. Some HPs identified with a calculus or cost-benefit analysis approach to decision making, where they weighed risks against benefits in making decisions about research. This implied that they considered decision making to be primarily a cognitive process.

When considering early phase studies of anticancer therapies, interviewees listed: i) disease-related benefits (e.g., disease response or relief of physical symptoms), and ii) emotional benefits (e.g., families deriving hope from trial participation; families perceiving a sense of altruism, in benefiting future patients and contributing to science, and trial participation as a means of creating legacy). HPs considered potential harms of early phase studies to include i) physical burdens (e.g. physical side effects, suffering and reduced quality of life) and ii) practical burdens (e.g. time spent in hospital, needing to take oral medications, and financial costs).

Interventional palliative care studies were seen similarly to early phase studies in terms of risks and benefits. HPs identified these studies as offering potential improvements in symptom management, with the possible costs of side effects that may impair quality of life.

HPs considered the risk-benefit profile for qualitative and experiential palliative care studies as distinct from that of early phase and interventional palliative care studies. In terms of benefits, HPs suggested that these studies could i) improve the quality of palliative care; ii) give voice to

children's perspectives about EOL care; iii) focus the family and their HPs towards quality of life, providing information that could guide supportive care; and iv) children may experience therapeutic benefit or enjoyment from taking part; while v) also benefiting from a sense of altruism and legacy, as with early phase studies.

Risks were also felt to be different from those of early phase studies. HPs worried that studies i) raising EOL-related topics, including death, could cause families distress, and ii) took valuable time away from families at the EOL. However, some HPs felt that the focus on the emotional harm of these studies was overstated, and benefits were underrecognized.

4.4.1.3.1 Perceived Prioritization of Survival-Focused Research

There was significant variation in perspectives regarding the priority given to different types of research by the oncology community. Many HPs felt that higher prioritization was given to research focused on cancer biology, or early phase studies, whose perceived end goal was improved survival. Some non-oncologists felt that this prioritization was because oncologists conducted or championed survival-focused studies, while others stated that this prioritization reflected parents' and research funding body interests in cure above all else. Other HPs stated that it was not just oncologists that valued survival foremost: survival was the primary focus of the hospital, and the broader field of pediatrics. This was reflected in the types of research published by major oncology journals and the awards made by the scientific and wider community. For example,

You may win the Nobel Prize for developing immune checkpoint inhibitors [an anti-cancer therapy]. You're not likely to win the Nobel Prize for developing a better antiemetic [a supportive care therapy] or understanding how families make choices around end-of-life care. (Staff Physician, H12)

Some HPs, including oncologists, disagreed, stating that all research could be valuable, depending on scientific merit. However, several oncologists made contradictory statements that while *they personally* valued qualitative or experiential palliative care studies, the oncology community might not. Furthermore, they expressed uncertainty about these studies, stating that i) the endpoints were 'softer', ii) they didn't generate findings that directly improved care and iii)

they perceived qualitative methodologies as being under-developed. Several participants, including fellows and staff physicians felt that conducting qualitative or experiential palliative care research could negatively impact HPs' career trajectories, highlighting a perceived lack of value of this research within the oncology community. However, other physicians disagreed.

4.4.2 Emotional Influences on Research-Related Decision Making

All interviewees richly described a complex emotional context where decisions were made about research. This context reflected the interrelated emotions of parents of children with cancer *and* their HPs. This emotional backdrop influenced decisions about research studies, and EOL decision making in general.

4.4.2.1 Uplifting Emotional Experiences for HPs

HPs described many positive emotional experiences in caring for children and families affected by cancer. All the HPs interviewed described their work in pediatric oncology as being meaningful and important to them. It was clear that many of these HPs perceived their work to be a vocation. These HPs derived satisfaction from close, long-term relationships with families and fulfillment in meeting their (HPs) own personal standards of high-quality care. Although they hoped to cure children, many HPs found a sense of purpose in alleviating patient and family distress and suffering, particularly towards the EOL.

Families' decisions for their child at the EOL influenced HPs' emotional experiences of caring for them. HPs were satisfied with many decisions that families made regarding research specifically, and care in general. They described situations where they were 'on the same page' as families regarding important decisions. In some situations, this meant that the medical team and the family elected for further anti-cancer therapy, but the cost-benefit analysis gave HPs the satisfaction that this would likely improve or not compromise the child's quality of life, and HPs believed that children agreed to treatment. In other cases, 'being on the same page' meant that a family and the team reached a point, at a similar time, where they prioritized quality of life over trial participation or further therapy. In both types of situations, HPs were fulfilled by being able to provide care and alleviate suffering, where possible despite advancing disease, in ways that they believed were appropriate.

4.4.2.2 Challenging Emotional Experiences for HPs

Participants also described challenging emotions in caring for children at the EOL. HPs experienced profound sadness in witnessing children and their families suffering from the physical and emotional consequences of worsening disease. As an example of emotional suffering, HPs perceived many parents to be anxious and overwhelmed by having to make decisions while experiencing sadness and loss.

Many HPs working in all roles experienced feelings of guilt, failure, and helplessness when a child could not be cured. Other HPs talked of experiencing self-doubt regarding decisions they had made previously if a child subsequently died. Paradoxically, several HPs acknowledged that deaths sometimes *felt* like a personal failure, even when they *knew* intellectually that the child's death was due to the limitations of modern medicine.

4.4.2.3 Relationships between Emotions, Decision Making and Communication

4.4.2.3.1 Concerns for Parental Hope and Legacy

Influenced by these challenging emotional experiences, HPs described their tremendous compassion for families who were suffering. For many HPs this gave rise to two related concerns. First, a concern for 'parental legacy': the idea that parents needed to live with their decisions after their child died, knowing they had done everything possible to save their child's life.

...these families are going to live with this experience for the rest of their lives, right? And so, you wonder sometimes.....clearly our first priority is the child, but that child passes away and the family lives on and they have to live with the chaos of that experience.....Recently we've acquiesced a little bit to families whose demands don't seem entirely in line with ours [e.g. for trial participation], in part because we realize that moving beyond their child's dying is going to be a whole lot harder if they feel that they weren't able to advocate for their child or they didn't do everything they could do to the last moment. (Staff Physician, H12)

Second, HPs showed concern for parental hope. HPs felt that parents needed hope to sustain them, with many HPs perceiving that early phase trial participation helped maintain hope. Some HPs believed that hopeful parents could still understand the poor prognosis. However other HPs worried that hope might motivate parents' ongoing need to 'try any option' choosing further therapy and trial participation, potentially sacrificing their child's quality of life close to the time of death.

Other HPs worried that compassion for families and concerns for parental hope led the medical team to go too far in accommodating family requests around care, at times perceiving that their colleagues 'lost' professional boundaries. Additionally, many HPs' concerns for parental legacy influenced these HPs to accept the parental need to 'try any option' for ongoing cancer therapy, including on early phase trials, even if they worried that continued anti-cancer therapy was not in the child's best interests. Some HPs talked of accepting parental decisions to avoid conflict with suffering families. Fewer HPs described the concern that if a child suffered when receiving cancer therapy at EOL, this may create a 'parental legacy' of regret.

4.4.2.3.2 HPs' Hopes

While HPs primarily focused their comments on parental hopes and their influences on decision making, it was clear that they experienced their *own* hopes when caring for children, and that HPs hopes were interrelated with, and may influence, parental hopes and decision making. One oncology fellow (H15) described wanting to be "a person of cure", indicating that they saw cure as a fundamental aspect of their identity, fueling their hopes that new treatments would succeed. However, oncologists also talked of moderating their excitement at the prospect of new treatments with reality, when making clinical decisions.

4.4.2.3.3 Influence of Emotions on Communication with Families

Emotional factors led many HPs to struggle to communicate with families about EOL research. These factors included hope, sadness, compassion for families, and HPs own discomfort with death. Fellows, oncologists, and nurses discussed their own personal difficulties in talking with children and families, while social workers and palliative care physicians perceived that their colleagues struggled with these conversations. Conversations about research generally took place between oncologists and families when early phase trial participation was being considered.

However, when palliative care studies were being offered, other HPs, including nurses, approached families, asking permission for researchers to contact them

Concerns about parents having what they deemed to be the ‘appropriate’ level of hope influenced oncologists’ communication with families about early phase trials. Many oncologists talked of balancing hope with ‘reality’, wanting to provide families with enough hope to cope with their child’s illness, but enough understanding to know that their child may not survive. In practice, many oncologists, and other HPs struggled with the challenges of communicating to titrate such a precise balance.

At times, concerns about hope and reality led oncologists to soften, delay, or avoid prognostic communication. HPs talked of communicating vaguely to avoid hurting families or even to ease HPs own personal discomfort with death. This reduced the clarity of communication. Some HPs worried that unclear communication could impede families from understanding the gravity of their child’s situation, influencing parents’ choices for ongoing therapy and early phase study participation at the EOL.

In the multiply relapsed patient, it's important to be clear that the expectation on this study is not curative, although I think families will often hold out hope, even though we've said that, right? ...Despite what we've said. And I don't necessarily know if everyone, if all my colleagues, actually, necessarily say that in the consent process. I think sometimes it's, sort of, allowed- like it's a benevolent ambiguity, right? They allow this hope that it may be curative. And I wonder if we were too realistic in our consents, we would probably never enroll a patient on a phase one trial. (Staff Physician, H9)

Many oncologists described taking great pains to present trial and other treatment options neutrally, allowing families to make their own decisions. However, many nurses, fellows, social workers, and palliative care physicians felt that oncologists’ hope to cure may affect families’ decision making. For example, they felt that oncologists who persisted in being hopeful may continue offering cancer therapy and trials towards the EOL, delaying the introduction of palliative care. Indeed, some oncologists talked explicitly of offering trials to provide hope.

Some HPs felt that oncologists' expressed or implied hopes and preferences were impactful, influencing conversations about trials with families, even when oncologists believed they were being neutral. These HPs felt that families valued their relationships with oncologists; wanted to be guided by them and sought to avoid offending them; with HP describing the oncologists as "the Gods around here" (Social Worker, H11).

Another social worker described some of the impacts of emotions on communication, below.

I think that (pauses) people get scared. It's hard (in a higher pitched voice) to have those conversations [open communication about prognosis]. It's emotional. It's scary to know where they're gonna go, right? Because once you're opening up those real big conversations. If you don't have the proper training or you're not open to having that conversation, it's scary 'cause you don't know where it's gonna go. And sometimes people worry that they don't want the families to lose hope. They don't want to break the- (moves hand from chest towards camera repeatedly) maybe I'm just projecting, but they don't want to break that trust that they've built with the family and think that the physician has given up hope or that the team has given up hope... also there's sometimes long-term relationships with families in hem/onc [sic]. It's different than some other areas of medicine where people have shorter relationships, so there's more attachment sometimes. So, people could have a harder time of accepting that even though they have boundaries, you still form an attachment to the child if you're treating them for many years.....And I think sometimes in the moment what I've also seen is when people go in [they] think they're gonna say it as it is, the language and the words you use are so important...in the moment when you're looking someone in the face and you want to really tell them something that is gonna be devastating, it's very hard. And then, you see the look in their eyes and then you change the tone, or you change the conversation, or you change the language even in the slightest bit (holds two fingers almost pinched together), but they hold onto that word and those words, right? So, what you say and what they hear are two different things. Or sometimes I've seen people sort of just (pauses) change direction based on the family's (pauses) emotions, maybe. Or just want to pack it in. (Social Worker, H32)

Many HPs believed that it would be challenging to discuss participation in palliative care studies exploring perspectives or decision making with some families, depending on their understanding of their child's prognosis and willingness to openly discuss EOL. For families who were 'not on the same page' as the health care team and were perceived as being 'overly' hopeful, discussing palliative or EOL care studies was seen to risk causing anger or distress. Several HPs discussed challenges around language, if words like 'palliative' were used to describe a study, worrying that specific words may upset individual families. In contrast to early phase studies that were seen as offering hope, potentially even delaying parental acceptance of a poor prognosis; discussing palliative care studies was seen as challenging as it could require acknowledgment of that poor prognosis.

You may need to change the language that you use to explain the research, depending on the family and where they're sitting at right now.....Different people interpret things a bit different, I had another family the day before [they] passed and they knew [they were] end of life and they...would talk about things that [they] wanted to do before [they] passed, they were very open to the words 'end of life'. But then if I compare that to this [another] family, they would never want to hear the words 'end of life'. (Pauses) Or 'palliative care' I think maybe could be used with this particular family because it's just the type of care you're providing but they don't like hearing the words like 'end of life'. I think it depends, you adjust the language used, depending on where the family is at. (Nurse, H34)

Emotional aspects of relationships between HPs and families were also felt to present a barrier to discussing research. Some families were felt to have negative relationships with care teams, for example, families who were angry, disruptive, or unwilling to be in hospital. One staff physician referred to these relationships as involving limited 'social capital', stating that in these circumstances HPs may choose to avoid 'optional' conversations about research, prioritizing 'essential' conversations about clinical care (H3).

4.4.3 Ethical Tensions in Research-Related Decision Making

4.4.3.1 Ethical Tensions

HPs were clear that they often agreed with families' EOL decisions about research participation. However, HPs were significantly concerned by a small number of situations, including specific situations where children participated in early phase trials. This included cases where HPs: i) believed that EOL trial enrollment would lead to suffering, or ii) worried about parental understanding about trial participation and prognosis, or iii) believed that a child's role in decision making was insufficient.

4.4.3.1.1 Believing that EOL Trial Enrollment would Lead to Suffering

The decision to enroll children in early phase trials or continue anticancer therapy towards the EOL was a common concern for interviewees. Specifically, HPs worried that children were exposed to potential side effects, despite a low chance of cure, and that their quality of life would suffer. Some HPs perceived that these decisions to continue ongoing therapy delayed the institution of palliative care and led to 'futile' suffering potentially close to the time of death.

4.4.3.1.2 Worrying about Parental Understanding of Early Phase Trials

Many HPs worried about parental understanding of the trials their children participated in near the EOL. These worries stemmed from concerns regarding i) parental overwhelm, ii) the complexity of information provided to parents about trials and iii) unclear communication (described above). Many families were perceived by HPs to be overwhelmed in caring for their child, and more so by the need to make EOL decisions. HPs worried that, given this state, families struggled to grasp or retain the information provided about trials. Additionally, HPs felt that the complexity of oral and written information given to families about trials, and the (increasingly) large number of trial and treatment options available, added to parental struggles to understand information. As described before, many HPs worried that unclear communication prevented parents from understanding the gravity of their child's prognosis, the likelihood of their child benefiting from study participation, and the purpose of trials, and that study enrollment created 'false' or unrealistic hope.

The challenge is [that] as much time and effort [as] the team spends with families to help them in their understanding, I (audible in-breath) I can't say that parents are always really processing that information, just given all that's going on, in truly informed consent. But I think every effort is made in trying to inform the child age appropriate[ly] as well as the parents or caregivers involved (Social Worker, H14)

4.4.3.1.3 Believing that a Child's Role in Decision Making is Insufficient

Although many HPs wanted to involve children in discussions about research, they described challenges in doing this. HPs experienced angst where they perceived that children were old enough or cognitively able to participate in discussions about trial enrollment but were not. This was usually because parents were perceived to conceal diagnostic or prognostic information from children or to restrict communication between children and their medical teams. In other situations, children did not or could not articulate their own wishes or chose to be uninvolved in decision making.

HPs, in particular nurses, expressed uncertainty in specific situations where they questioned children's 'true' wishes regarding research that included ongoing anticancer treatments. Implied in this concern was the idea that children were 'going along' with parental wishes, and if given the choice, they would not choose further anticancer therapy. In contrast, a staff physician suggested that in expressing uncertainty about children's wishes, HP's may be projecting their own feelings onto the children involved, again highlighting the potential impact of HPs emotions on their experiences.

In other situations, HPs struggled where they perceived that a child's expressed wishes were not being followed, describing this situation as a child's 'voice not being heard'.

4.4.3.2 Conflicting Ethical Principles

4.4.3.2.1 Autonomy vs Beneficence and Non-Maleficence

The situations that caused the most concern for HPs involved conflicting ethical principles. HPs felt that parents had the right to autonomy or at least to participate in decision making,

particularly towards the EOL. One staff physician (H5) talked of having been trained that decision making *should* be shared between parents and HPs, making it feel “*wrong*” to do anything else. This prioritization of parental autonomy was strongly influenced by concerns for parental legacy, described before. However, HPs worried that parental choices would lead to children suffering and worried that they (HPs) ought to make “*paternalistic*” decisions for children and families, protecting them from potential harms of research participation. In this way, the desire to promote parental autonomy conflicted with the need to ensure beneficence and non-maleficence to the child.

4.4.3.2.2 Parental vs Child Autonomy

HPs also believed that children had the right to voice their concerns, and be ‘heard’, if not to exercise their own autonomy, when capable. This led to a small number of situations where parents’ and children’s rights to autonomy conflicted.

As described before, some HPs worried about children ‘going along’ with parental wishes for trial participation. However, other HPs stated that a child had the right to comply with parental wishes, even if parental wishes conflicted with the child’s own preferences. This was perceived as another expression of children’s autonomy.

Several HPs felt that despite their impulse to make ‘paternalistic decisions’, ‘protecting’ children, or their wish to promote children’s autonomy, ultimately it was parents’ wishes that ‘won out’. Again, HPs deferred to parents’ wishes, motivated by concerns for parental legacy, but several HPs including oncologists, wondered if they sometimes went too far in the name of parental autonomy.

4.4.4 Influence of Professional Role on Experiences of Decision Making

4.4.4.1 Oncologists as Decision Makers about Early Phase Trials

HPs’ professional roles determined their involvement in decision making about early phase trials. This in turn affected experiences of decision making. The primary staff oncologist, who had ultimate responsibility for each patient, led decision making for that child. Decision-making

deliberations were often brought to a broader group by the primary oncologist, for example, during interprofessional rounds or informal conversations. Fellows, social workers, some palliative care physicians, and specialist nurses (e.g. research nurses or nurse practitioners), were present. Often, once a recommendation was formulated at rounds or by the primary oncologist, potential therapeutic options, including trials, were discussed with parents. Discussions with families typically involved oncologists, although sometimes fellows, social workers, and specialist or bedside nurses attended.

All oncologists talked about involving and valuing the contributions of non-oncologists in discussions about trial participation. While some non-oncologist HPs felt that they could raise concerns and question decisions, several non-oncologist participants, including nurses, fellows, and social workers, felt that they had limited ability to influence decision making.

4.4.4.2 Having a Limited Role in Early Phase Trial Decisions as a Non-Oncologist

Bedside nurses played a very limited role in decision-making conversations about early phase studies. These nurses talked about logistical and other reasons why they were not present for discussions at rounds or with families. For example, nurses often worked inside patient rooms and were not physically in the main area of the floor when the rest of the team decided to meet and discuss patients. They may, therefore, not be aware of, or be invited to join, discussions. Nurses were unable to leave the floor for long periods of time whilst on shift, meaning it was difficult to attend rounds or discussions about patient care, even if they were aware that discussions were occurring.

Many bedside nurses only heard in passing about decisions that had been made, for example, when chatting to colleagues during the workday. Several nurses mentioned or identified with the idea of ‘hearing whisperings on the floor’; ‘backroom’ discussions only involving nurses, usually about decisions that they weren’t involved in making, but felt were ethically challenging. On other occasions, nurses learned about decisions families had made, when hearing that they were expected to administer a treatment or reading their patients’ chart. Some nurses acknowledged that they occasionally made assumptions about how and why decisions were made, since they weren’t involved in decision making. They described decision-making processes as ‘opaque’.

Not being present for conversations led some nurses to speculate that parental lack of understanding may reflect a failure of oncologists to be open and clear with parents about the prognosis and the low likelihood of benefit from ongoing therapy or trials.

Social workers talked about sometimes being included in conversations about research studies, but not being asked to participate on other occasions. They similarly described decision making as being opaque at times.

When asked about who should be involved in decision making, many nurses and social workers stated that they didn't have the medical knowledge to contribute to discussions about trial participation or ongoing therapy. However, both nurses and social workers wanted to better understand how and why decisions were made, and to be present for discussions. Furthermore, social workers stated that they had intimate psychosocial knowledge of families. They hoped and believed their perspectives were respected by their colleagues and wanted these perspectives to be incorporated when decisions were made. Some nurses stated that their role was to follow orders rather than to make decisions.

...that's a choice that I made when I chose to be a nurse. Different people in different positions have different roles and responsibilities and sometimes as a nurse, you are the implementer, but not necessarily the decider. For me, that's OK. It doesn't necessarily reduce the distress at being an active participant in a situation of profound suffering, right? That's still there. But in some ways, it's part of the reality of being a bedside nurse. What would help is transparency around how the decision was made and how the counseling was performed, what and why the decision was made, in the way that it was. So, sometimes the opacity can be troubling because you have all of these ideas in your head about what may or may not have happened, but you don't really know necessarily. (Nurse, H36)

It should be noted that there was variation in perspectives around decision-making roles, and that many non-oncologists and oncologists were satisfied with decision-making processes and their roles within them.

4.4.4.3 Acting as a Gatekeeper for Palliative Care Studies, as a Nurse

Nurses, including bedside nurses, were more commonly involved in patient recruitment for non-early phase studies, such as qualitative, experiential and symptom management studies.

Researchers involved in palliative care studies may come to the inpatient floor or outpatient clinic and consult the nurse taking care of a patient, before approaching the family directly or requesting nurses to speak to the family on their behalf.

Many HPs, including nurses, raised or identified with the idea of ‘gatekeeping’, the sense that they could allow or prevent researchers from meeting with families to discuss studies. HPs described the considerations that they made when deciding whether to ‘open the door’ to researchers. These considerations included informal assessments of issues including family-related factors (e.g. how the family was coping socially, emotionally, and physically; the families’ understanding of their child’s illness and prognosis; recent events in the child’s disease-course such as a new relapse, and predictions of how interested the family might be in a study). Relationships with families were an important consideration; families who were angry or dissatisfied with care, were considered ‘less suitable’ for recruitment. HPs also considered study-related factors, such as the inclusion criteria, and their own perceptions of the scientific value and benefits and burdens of the study.

Many HPs felt that there were advantages to gatekeeping, primarily, protecting families from the ‘intrusion’ of researchers into their private space and saving families from the added burdens or distress of talking to researchers. However, some HPs wondered how accurate their own assessments of family interest in studies may be. Many HPs preferred to introduce families to the researcher, or the study, so they could make their own choices, rather than to decline on families’ behalf. Again, this reflected a desire to promote autonomy, in conflict with the desire to protect families from perceived burdens of research.

4.4.4.4 Perceived Hierarchy

There were varied perceptions around hierarchy in interprofessional teams. Oncologists did not feel that their teams were hierarchical, and many non-oncologists agreed with this.

However, some fellows, nurses and social workers felt that they were prevented by hierarchy from contributing to discussions and decision making. Hierarchy was also mentioned by a staff physician (H5), although they described other HPs as experiencing this, not themselves. When discussing hierarchy, nurses and fellows described their roles as being to implement oncologists' orders. Some felt unable to question decisions. Other nurses spoke of being unsure about whether they could refuse to implement specific orders that they felt were ethically questionable. However, some nurses cited a specific example where colleagues refused to administer chemotherapy to a child at EOL, with one stating that it was a nurse's license 'on the line' if they implemented an order that was not ethically defensible.

4.4.5 Impacts of Providing Emotionally and Ethically Challenging Care

4.4.5.1 Negative Impacts on HPs and Patient Care

HPs, across professional roles, identified negative personal impacts of involvement in ethically challenging cases where children participated in early phase trials. These impacts included stress, frustration, and burnout and are described below. Other HPs felt that team dynamics suffered when concerns about EOL decisions were limited to 'backroom' conversations and not openly discussed within the interprofessional team. A minority of HPs found that their ability to maintain therapeutic relationships and care for families was negatively impacted by situations where they were 'not on the same page' as families regarding EOL choices, particularly if families were perceived to be pushing the team into providing ongoing trial options, despite the preferences of the HP team.

4.4.5.2 Influence of Professional Roles on the Impact of Challenging Cases

Nurses, who spent considerable lengths of time at patient bedsides, witnessed suffering in a closer, more intimate setting than their colleagues and more acutely experienced ethically challenging situations. While they did not want more decision-making responsibilities, many nurses were extremely distressed when implementing decisions that they felt were ethically challenging, for example, administering a trial treatment they didn't agree with. Several nurses felt morally distressed by the belief that they contributed to a child's suffering. Many nurses

talked of having taken up a new role to allow them to continue in oncology nursing, for example, moving part-time to the clinic instead of working full-time on the inpatient floor. Other nurses described high nursing-staff turnover, which they perceived to be stress-related.

Knowing that you are actively giving a child this drug that likely will cause these problems. Even things like expected myelosuppression [a common side effect of chemotherapy] but that can lead to infection, which can ultimately cause the death. Especially when their bodies are not able to fight back. It's hard when the child passes away from one of the complications from that drug. And that's hard because they're not passing away because of the cancer, that's not what was the ultimate cause of their death. And it's something that as a nurse, you are signing off and you're actively giving. That is very hard to wrap your head around. I don't think that we necessarily think we caused the death because it's not the same as missing something that led to a problem, but you still are the one that's actively hanging that bag of chemo[therapy] or that kind of thing. It weighs on you, your actions, and I've seen the effects that it had on nurses that have been in those situations where they're like, 'Wow. I was part of that. I kind of fed into that and let it happen', which is difficult when, we're given orders, and we're expected to follow them. But being the person who does it can be hard. (Nurse, H30)

While less frequently at the bedside, and less closely witnessing the impact of children taking part in studies, all other types of participants, including oncologists, spoke of struggling with moral distress due to ethically challenging cases.

4.4.5.3 Coping with Emotional and Ethical Challenges

HPs used several approaches to manage the personal impacts of providing care in challenging circumstances. For example, many HPs talked about 'separating' their own emotions from a case and choosing to 'accept' parental decisions to proceed with a trial even when HPs did not feel it was appropriate. Acceptance could also mean acknowledging that you had done everything you could to influence a parental decision. HPs reframed decisions that they found troubling, choosing to see these decisions as an expression of parental autonomy and need for parental legacy. Several physicians (oncologists, fellows, and palliative care physicians) described a sense of moving on to the next patient, after the death of a child. They contrasted this with the experience of families, who they perceived, grieved forever. However, oncologists' own descriptions of their sadness and grief at losing patients, particularly in ethically challenging cases, suggests that they might not move on as painlessly as they described.

Oncologists talked of ‘bringing on board’ team members, by discussing decisions that had been made with colleagues, particularly if challenging. Team approaches had been instituted to address the impact of ethically challenging cases for HPs. All types of HP mentioned interprofessional debriefs that occurred before and after death. Many HPs appreciated these debriefs, although some bedside nurses were unable to leave patient care to attend debriefs, and some non-oncologists hesitated to ‘speak up in these meetings.’

4.5 Discussion

We sought to explore EOL research-related decision making from the perspectives of HPs. These HPs described the vital necessity of research for ongoing progress in oncological, supportive and palliative care. However, many interviewees expressed concerns regarding the implications of research participation for children and families whom they considered to be vulnerable.

4.5.1 Implications of Perceiving Early Phase Studies as Treatment, not Research

Although HPs acknowledged EOL early phase studies as being research, it was interesting to note that they perceived these studies primarily as treatment options for children without other therapeutic possibilities. Like other EOL research, the purpose of early phase studies of anticancer therapies is to provide information that guides the care of future patients. While it is possible that study participants will benefit from involvement, early phase studies seek to provide information about toxicity and dosing^{4,21,26}. This raises the question of why HPs chose to conceptualize these studies in this way.

One straightforward answer to this question is that early phase studies are perceived as therapeutic options at the EOL since they are used in this way: they are offered to children as last treatment options when they have exhausted standard choices.

However, given concerns about participant vulnerability; HPs discomfort with burdening such families in the name of research; their close relationships with and compassion for these families,

it is worth considering whether it is emotionally easier for some HPs to conceptualize early phase studies as therapy and a way of offering hope to families. Whereas the intent of therapy is to benefit the patient receiving it, the intent of research is to benefit other patients and to contribute to science. By conceptualizing studies as therapies, HPs can feel that they are offering something to benefit families, as opposed to research which is conceived to be making demands of them at a difficult time. For HPs who care deeply about their patients and families, it may align better with their ideas about themselves and the work that they do, to perceive trials as therapy.

Considerations of EOL research as therapy are relevant to discussions of therapeutic misconception and misestimation^{8,9,26,118}. If parents have misconceptions about the purpose of research, and HPs think of early phase studies as treatment rather than research, it is conceivable that ways of conceptualizing and possibly communicating about trials may be contributing to these misconceptions.

4.5.2 Perceptions about Palliative Care Studies: Implications for Recruitment

In contrast, HPs appropriately conceptualized palliative care studies as being research. This is of significance, since conceptualizing these studies as research and therefore, primarily intended for the benefit of science, may influence some HPs to under-estimate potential benefits to patients and families and place their focus on possible burdens. This may explain some of the gatekeeping behavior that HPs talked of engaging in.

Challenges in conducting pediatric palliative care research are well-documented^{30,32,130}. In previous surveys, researchers described multiple barriers to pediatric palliative care studies including gatekeeping by HPs, who worried about participant burdens^{131,132}. Crocker *et al* explored reasons why HPs failed to invite parents to participate in a pediatric palliative care study. They identified several factors including HPs' assessments of the current wellbeing and circumstances of the family to be recruited and the families' expected reaction to the invitation³¹. Our interviewees made remarkably similar assessments regarding families when considering whether to gatekeep. However, many of our interviewees identified that their assessments may

not always be accurate, and others spoke of allowing families autonomy to make their own decisions.

Our study participants described families' hopes and sensitivities about palliative care as making it hard to broach participation in palliative care research. However, given the emotional impacts of their work, and the difficulties that HPs described in communicating with families, our findings raise the possibility that HPs' own emotions such as hopes, feelings of failure and discomfort with death may be an unrecognized cause of reluctance to approach families about palliative care studies.

It should be noted that while HPs may worry about the burdens of palliative care studies for families, there is growing evidence that children, siblings and their parents find participation in these studies to be valuable and meaningful^{30,34,122}. There is also evidence to suggest that HPs place more emphasis on the potential burdens of studies than families who may find therapeutic and other benefits in study participation¹²². Additionally, some HPs' perceptions that qualitative and experiential studies lack sound methodology and are less impactful on science, may present further challenges for patient recruitment, since these HPs talked of considering scientific benefits when making decisions about gatekeeping.

4.5.3 The Under-recognized Role of Emotions in Decision Making

We sought to understand processes of decision making about EOL research. However, we did not anticipate the significant influence that emotions have in these processes. When asked about how they made decisions, some interviewees explicitly or implicitly talked about cognitively weighing the risks and benefits of research, similarly to how risks and benefits are listed on consent documents for medical treatment.

The idea of decision making as a cognitive process is reflected in the scientific literature. Much of this research originates from the fields of behavioral economics and consumer psychology¹³³. This literature explores how the attributes of therapeutic options influence individuals' preferences when making treatment decisions¹³⁴. For example, in a hypothetical decision-making study, a decision about participating in EOL research may be broken up into constituent

characteristics, such as the percentage chance of experiencing side effects or cure⁷⁰. Strength of preference for a treatment option may be measured by systematically altering the probability of benefit or harm of one of the treatment options to identify when participants choose the alternate treatment over that initially chosen. While these studies provide informative quantification of decision making, it seems unrealistic to imagine that decision making about children at the EOL can be captured in all its nuance and complexity solely through quantitative means. Our use of inductive interpretive qualitative methods allowed us to explore some of these complexities in a richer way, describing interrelationships and challenges around emotions and communication that exist between HPs and families. Our findings suggest that emotions play an important role in decision making as evidenced by the ways in which many HPs talked about the intense emotional context of their work, the influence of emotions on their communication about EOL choices, and how these patterns of communication may affect the decisions that were made by families. These findings are consistent with a growing literature suggesting that emotional influences play an important role in decision-making processes¹³⁵.

4.5.4 Dialectic Tensions in EOL Care and Research

Many interviewees experienced opposing tensions in their work, relating to their ability to meet their personal standards of high-quality care, their communication with families and their support of parental autonomy.

Relational dialectics is a communications theory that describes these kinds of tensions in personal relationships^{136,137}. As a social constructivist theory, relational dialectics sees communication as an active process through which we create meaning, and thereby construct relationships and our social worlds¹³⁸. This theory, proposed by Baxter and Montgomery, describes how human interactions are characterized by dialectic tensions; competing perspectives that are also interdependent, and in constant interplay. While others have been described, Baxter has underscored the “big three” tensions that arise in a range of types of close relationships: autonomy and connection with others; expressiveness and protectiveness in communication; and certainty versus uncertainty in relationships¹³⁸.

For example, a teenager may desire independence from their parents, while also seeking closeness to them, reflecting a dialectic tension between competing perspectives of individualism versus conceptualizations of family. An individual may experience a dialectic tension, or tensions may occur between more than one person in a relationship. People navigate tensions in relationships that change over time; these tensions do not resolve but shift. For example, they may feel more strongly drawn towards autonomy in some moments, and connection in others, but both forces remain present. Our communication about dialectic tensions demonstrates how these contradictory ideas compete.

Relational dialectics theory has most commonly been applied in studying family relationships¹³⁶⁻¹³⁸. However, studies have explored dialectic tensions in healthcare, including at the EOL¹³⁹⁻¹⁴². Amati and Hannawa describe dialectic tensions in the EOL care of adults, based on their own study and pre-existing literature¹⁴². Several of these tensions align with our findings. We build on their work by identifying dialectic tensions in EOL decision-making about children's participation in research, an area where these tensions have previously been unexplored. Furthermore, we identified new types of dialectic tensions and some contributing discourses that underlie them.

Amati identified the tension of 'desire versus ability'. In our study, this applies well to the tension of HPs wanting to ease children's suffering, and provide what they believed was high-quality care, but being limited by the constraints of modern science and family wishes for ongoing trial participation.

We identified a dialectic tension related to openness in communication, experienced by HPs struggling to communicate with families about hope versus reality. This tension aligns with dialectics described by both Amati and Baxter as 'to tell or not to tell'^{138,142}.

Lastly, we identified several tensions relating to autonomy, with HPs: i) wanting to promote parental autonomy to make choices versus a desire to protect children from the consequences of parental decisions; ii) wanting to promote parental autonomy versus promoting children's autonomy, where there was a difference of wishes; iii) wanting to respect parental autonomy to restrict information provided to children versus believing (capable) children had the right to receive information regarding their prognosis and decision making; and iv) not wanting a child to

suffer by ‘going along’ with parental wishes for ongoing treatment versus believing a child should have the autonomy to sacrifice personal comfort for their parents. In most cases these dialectical tensions resulted from a push and pull between the prioritization of personal autonomy, a perspective of individualism, versus a duty to protect and be paternalistic over children. In other situations, the tension was between children’s and parents’ autonomy. Building on Baxter’s work describing tensions involving autonomy, Amati, critically, described similar situations where HPs and adult patients had differing wishes for ongoing treatment as a ‘hierarchical struggle’ between physician-centered vs patient-centered control^{138,142}.

While HPs described tensions between children’s and parent’s needs in relationships, it was often the perspectives of parents that were prioritized by HPs over those of children. This was motivated by compassion for parents, who would survive with the legacy of their child’s death. Similarly, perceptions of these parents as being vulnerable in general, and specifically at EOL, contributed to the desire to protect families. However, despite often taking a polar position of privileging the parental perspective, HPs struggled with these decisions and experienced these struggles as ethical tensions and moral distress.

Eaton Russell applied relational dialectics to her study of parent-adolescent communication in pediatric oncology¹⁴³. Interestingly, she described vulnerability and resilience as being a dialectic tension that overlapped with all the other dialectic tensions in that study. In this case, children with cancer were perceived by their parents to be emotionally vulnerable, while parents were perceived as similarly at risk by their sick children. This restricted communication in some families, so that parents and children hesitated to share their feelings with each other about ‘difficult’ topics, like early phase trial participation, fearing that to do so would risk causing the other to be distressed.

Eaton Russell’s findings make a parallel with our study, where perceived vulnerabilities limited communication between HPs and families. Additionally, HPs in our study described situations where, either parents restricted conversation between HPs and children, or children and parents failed to communicate openly with each other. Interestingly, while Eaton-Russell’s study identified vulnerability and resilience as being in dialectical tension, our participants did not

explicitly focus on families' resilience. However, HPs preoccupation with parental hope suggest that they hoped to foster familial resilience.

4.5.5 Decision-Making Challenges for Interprofessional Teams

Medical care is increasingly provided by interprofessional teams. In pediatric oncology, these teams typically include physicians, nurses, and allied health team members from disciplinary backgrounds including social work, pharmacy, occupational and physical therapy plus palliative care specialists. Interdisciplinary collaboration within interprofessional teams has been recognized by international societies including the World Health Organization as making an important contribution to the provision of high-quality, holistic, patient-centered, medical care, through the incorporation of interdisciplinary expertise and perspectives¹⁴⁴.

Healthcare teams have traditionally operated around hierarchical structures, with physicians taking responsibility for leadership and decision making. There is evidence to suggest that these hierarchies can negatively impact the functioning of teams, by creating an atmosphere where team members towards the bottom of hierarchies feel that their contributions are less valued and where they do not feel able to voice concerns, hindering the productive resolution of conflicts¹⁴⁵.

Our study sample was not unified on this topic; only a minority of participants described hierarchy as influencing decision-making processes. However, while other participants denied the existence of hierarchical working practices, they mentioned ways of working that may have been so, for example, nurses and social workers not being included when decisions about early phase trial participation were made. There are several possible reasons for these differences in perspectives. It may be that hierarchy wasn't a common problem in this setting, or that there were team or relationship-specific hierarchies at play in a small number of cases. However, there are other possible explanations. Hierarchical working may be ingrained in practice in ways that are unrecognized by HPs. For example, physicians leading teams may lack awareness of their hierarchical ways of working¹⁴⁵. However, we did not set out to explicitly study hierarchy, and further focused research is needed.

Despite the lack of clear hierarchies, it was evident that decision-making processes around early phase studies were largely the realm of the oncologists. Oncologists talked about incorporating non-physician perspectives in decisions, but several non-oncologists perceived their role in decision making to be limited. Interestingly, most non-physician HPs did not believe that this should change. However, their experiences of ethical challenges were affected by their roles in decision making. Many individuals who were not involved in decision making, but who implemented decisions or supported families, perceived decision-making processes as opaque, worried about the quality of communication, and had ethical concerns about decisions that were made. The nurses who were most closely and intimately involved with patient care, and who were present at the bedside to witness the consequences of decision making, often experienced these situations more acutely than their colleagues, although all types of participants described experiences of moral distress. Our findings align with those of Matthews *et al*, who identified that measures of moral distress were higher for members of the health care team such as nurses, fellows and social workers, who were not in decision making roles¹⁴⁶.

4.5.6 Returning to the Conceptual Framework

As described earlier, we used a conceptual framework to identify knowledge gaps in the literature and to guide the choice of interview questions. Consistent with our inductive approach, we did not refer to the framework until the analysis was completed. On returning to the framework, we note that it provided a useful map of the previous literature, and a helpful starting point for the study. For example, the framework mentioned the impact of EOL research-related decision making for HPs. However, our qualitative study built on this by identifying differences in impacts for HPs depending on their roles and involvement in decision making, the interprofessional tensions involved and the severity of the impact on HPs and teams. Additionally, while the framework identified emotional influences on decision making, the emotions under consideration were experienced by the families involved. A novel finding of our study was the influence of HPs' own emotions on the research decision-making process.

4.5.7 Implications for Training and Practice

As with other interpretive descriptions, our study was intended to produce research findings that can be used to inform clinical practice, specifically regarding research-related decision making at the EOL. Below we have outlined suggested implications of our findings for the training and practice of HPs working in pediatric oncology. While these implications are inspired by our interviews with study participants, they are our own suggestions intended to address issues that were raised by interviewees.

- i) HPs working in pediatric oncology should receive training and support to help them manage the emotional demands of their work and cope with its ethical tensions, particularly as they relate to research participation.
- ii) Training should include discussions of how emotions such as sadness, grief, compassion, and hope can influence decision-making processes and experiences of decision making.
- iii) Training and support should ideally be interprofessional and provide a forum for HPs across professional roles to share their experiences and the challenges they face, specific to and shared across roles, with the intention of building shared understanding.
- iv) Training should also include specific communication skills education and practice and should discuss how to deal with conflict between HPs and with families.
- v) Interprofessional teams should pay attention to how they include team members in decision-making processes and communicate within teams about decisions that have been made, particularly those that may be ethically challenging. Given the difficulties of working as large teams, with frequent shift changes, written documentation of how, why and what decisions have been made is an important component of communication.
- vi) Researchers should consider and address concerns that oncology HPs hold about palliative care studies. It may be helpful for palliative care researchers to collaborate

with oncologists in developing studies. Additionally, researchers should ensure that they articulate the potential benefits of their work, not only for the field of oncology but also for their participants. It may be helpful to cite previous literature that describes participant perspectives on palliative care studies. Researchers should be prepared to articulate the robustness of their methodology to address oncology HPs' concerns and unfamiliarity with these methods. They should also consider the perceived harms of palliative care research for patients and describe how these harms will be avoided.

4.5.8 Strengths and Limitations

A particular strength of this study was our use of inductive qualitative methods, but with the incorporation of previous literature and theory in the design stage. This allowed us to build on previous literature, while identifying novel findings grounded in our data. Using qualitative methods allowed us to provide a more nuanced description of the challenges inherent in decision making, exploring the interrelationships between parent and HPs emotions, the influence of emotions on communication and decision making, and experiences of decision making. A particular strength of this study is our diverse sample, with varying levels of experience and areas of practice. By including HPs in different roles, we were able to explore variations in perspectives, adding credibility through comparisons across HP roles.

In terms of limitations, firstly, while we included HPs across different roles, we included small numbers of palliative care physicians and social workers, given the size of these groups in the department. Additionally, the richness of the study would have been increased by including other HPs such as physician assistants, pharmacists and child life specialists. Secondly, a study about moral distress in pediatric oncology was performed in the same department, overlapping temporally with our study. This may have brought this subject to the minds of interviewees. Finally, this study was set in a single oncology center. However, we believe that the findings and the contextual description we have provided, give our study broader relevance.

4.6 Conclusions

Decisions about research participation for children with cancer at the EOL occur in an emotionally charged environment that influences communication and decision-making processes. HPs experience dialectic tensions in caring for children as decisions are made about research. These tensions are experienced as ethical struggles and at times, moral distress. Members of interprofessional teams who are less involved in decision making, but who implement decisions that are made, and closely witness the results, may particularly struggle. Focused interventions are needed to help HPs providing care in this challenging context.

Table 4.1. Participants' Demographic Characteristics

Characteristic	N=35 (%)
Gender	
Female	21 (60)
Male	13 (37.1)
Response not provided	1 (2.9)
Ethnicity	
East Asian/ South Asian	4 (11.4)
Middle Eastern	2 (5.7)
White	26 (74.3)
Other	2 (5.7)
Profession	
Oncology Nurse	12 (34.3)
-Bedside nurse (inpatient or outpatient floor)	6
-Nurse practitioner (in sub-specialist team on inpatient floor or outpatient clinic)	3
-Research nurse	1
-Clinic nurse (working in sub-specialist team)	2
Oncology Fellow	5 (14.3)
Oncology Staff Physician	10 (28.6)
Palliative Care Physician	4 (11.4)
Oncology Social Worker	4 (11.4)
Years in Practice in Oncology (median, IQR)	13 (5.0 to 23.8)
Current Areas of Oncology Practice*	
Central Nervous System Tumor	20 (57.1)
Leukemia/Lymphoma	19 (54.3)
Solid Tumor	22 (62.9)
Hematopoietic Cell Transplantation	11 (31.4)
Current or Previous Role Includes Conducting Research	
Yes	26 (74.3)
Current or Previous Role Includes Conducting Research with Children Receiving Palliative or End of Life Care	
Yes	11 (31.4)

* Interviewees could have more than one area of current oncology practice

Table 4.2. Representative Quotations

Risks and Benefits of Research Participation at EOL	
Importance of EOL research	<p><i>“I think it's imperative, to be honest with you. I think that research, whether it's formal or informal, has been the way that medicine and healthcare and outcomes have moved forward and how we get better at whatever it is that we're doing. By looking at things from a systematic way and to not include patients who are affected or afflicted by these conditions in this research, I feel like it's moving forward with one, if not both, arms tied behind our backs. We have to include them. It's ultimately them that we're trying to help and to improve, and to not, include them in research is something that, I think that we would be, we would just be missing a huge opportunity” (Staff Physician, H2</i></p>
Burdens of EOL research for families	<p><i>H3: “every time I'm calling this family, I'm calling them with a list of things that they need to do...I'm constantly asking them to do (things) or telling them about other things to put on to their calendar, and for me to call and have one more thing to ask them that is not strictly necessary, feels... I feel uncomfortable with adding something else in my list of requests to this family. “</i></p> <p><i>I: “Sort of adding to the work of having a child who's coming toward the end-of-life, does that sound right?”</i></p> <p><i>H3: “Yeah, you nailed it. That's it exactly. That it's one more thing for a family for whom there are already too many things.” (Staff Physician, H3)</i></p>
Weighing risks against benefits	<p>Weighing Risks against Benefits</p> <p><i>I: “One of my other participants talked about a sort of calculus that they go through when they think to themselves, is this a study that we should be presenting to this family or not? Does that sort of calculus resonate with you? H23: (nodding while the question is being asked) Yeah, to a certain degree it does. Going back to the point that, there could be six or seven different studies that this particular patient may be eligible for and there has to be some way of determining a rank order or priority.” (Staff Physician, H23)</i></p> <p>Risk-benefit profiles for early phase studies</p> <p><i>“we may be doing a bit of a dance between (repeatedly lifting up hands alternately, palms facing up), a trial medication, a new agent, so a phase one treatment, but also trying to balance that with the quality of life for their care and day to day, and (pauses) and figuring out that focus and figuring out how to support and (pauses) (chuckles) they're loaded statements, 'cause I was going to say 'in a positive way', but how do we determine what 'positive way' is? (Social Worker, H25)</i></p> <p>Risk-benefit profiles for qualitative and experiential palliative care research</p> <p><i>“...families need to know that even studies where you're just asking their thoughts and opinions, at a tremendously vulnerable time of their life, could still be tremendously <u>hurtful</u>, right? ...You could also potentially imagine some benefit coming out of it. Some people may actually find that a useful exercise to go through.....There is still risk of harm, but my sense is the stakes are different. The likelihood of serious harm is less. There's probably still some risk</i></p>

	<p><i>of burden and emotional price of doing one of those studies, but my sense is for most studies it would be far less significant and probably easier to deal with (than an early phase study). (Staff physician, H12)</i></p> <p>Perceived prioritization of survival-focused research <i>“Maybe the way people are thinking about it is, what kind of journals do you publish these studies in, right? And then relating that to impact factors and impact to the community and sexiness of that research and potential, phase one. Like the biggest, like the new best drug, CAR T, when those phase ones were done and they were all awesome, right? Huge impact, glamorous like Hollywood, these are amazing studies. It's going to <u>advance</u> outcomes, right? That's the golden end point that everybody wants.I think in some people's minds just get viewed- just get lumped with softer kind of stuff, softer kind of research, not as sexy, not as hard endpoints.....I would think people would potentially view some of these (clicks tongue) studies as not being viewed as impactful to the community and, therefore, maybe not published as highly and, therefore, not as, coming back to the investigator, not as quote beneficial to them academically, overall.” (Staff Physician, H17)</i></p>
<p>Emotional Influences on Research-Related Decision Making</p>	
<p>Uplifting emotional experiences for HPs</p>	<p>Satisfaction <i>“End-of-life care is difficult when people are not on the same page and when there’s not a lot of effort taken to ensure that people are on the same page. Sometimes, that's easy to do. I've been on call before on a weekend, I remember when a patient was recovering from a procedure just to help her pain and she had been anesthetized for that, and she was having a lot of trouble recovering from the anesthesia and was admitted to (name of floor) and I was worried that she might not actually recover. And there had not been an end-of-life care already done, even though things were going in that direction. And this mother over the course of the weekend, became increasingly open to the fact that we would want to keep her daughter comfortable, and so that ended up being a nice situation.” (Fellow, H4)</i></p> <p>----- -----</p> <p>Fulfillment <i>“My favorite parts of the job are definitely being able to make this easier for the kids and the families in any way at the moment, whatever part of their disease trajectory they’re in... That can be really rewarding, and I really do love that part of the job as well.” (Nurse, H33)</i></p>
<p>Challenging emotional experiences for HPs</p>	<p>Sadness <i>“The hardships that these families are experiencing, and all of the families that are on the unit.... hearing every little bit of bad news, it weighs on you whether you realize it or not.....particularly with children, It seems so unnatural to witness young children dying. And taking them to the morgue and things like</i></p>

	<p><i>that, it feels like it shouldn't be happening. So, I think unconsciously, even, it really weighs on you.” (Nurse, H30)</i></p> <p>-----</p> <p>Guilt <i>“...to me, a cure, a victory’s not because of me. I don't want to take the credit, and I like when the child goes back to a normal life....But at the same time, when the child doesn't make it, I feel the guilt of that. It's this ambiguity here, which is you are never happy with what you have done. But it's something that I have accepted here. Knowing that, yes, I know that I'm responsible for the failure, but I don't take it as a personal responsibility.” (Staff Physician, H28)</i></p> <p>-----</p> <p>Failure <i>“Nobody wants to give up on their patients, right? I think everybody wants to feel that they've done the very best that they can and had offered everything they possibly can [including a trial]. It's not easy to say that it didn't work. I think it's a feeling like we <u>fail</u>- I mean, we haven't failed, but it's a feeling like we've failed this child or failed this family, right?’ (Social Worker, H11)</i></p>
<p>Relationships between emotions, decision making and communication</p>	<p>Concerns for Parental Hope and Legacy <i>“I think that a fair amount of patients on phase one trials do hang on to hope that they will survive because of their phase one drug, even though that's not really the goal of a phase one study.” (Oncology Fellow, H4)</i></p> <p>HPs’ Hopes <i>“I get excited about it too. I mean, a new drug, (smiles) I'm ready to use it. And then, oh yeah, we have to (laughs) still figure out whether it's actually going to be effective.” (Staff Physician, H23)</i></p> <p>Influence of Emotions on Communication <i>“A good oncology team sets these expectations from the beginning and has open conversations about end-of-life and about things not going well and things not working and the cancer progressing and what will we do if this progresses, and all of that.....I have the sense that either because parents don’t really want to hear about some stuff and we are also not super comfortable in some situations discussing it, we get into this snowball effect of the parents don’t really want to hear about it and we’re not comfortable, so let’s just go with the flow. And then when the situation happens that the child progresses or there’s another relapse which we were expecting in this situation, parents don’t accept this. They’re still in that phase of ‘we’re going, we’re curing this’” (Fellow, H7)</i></p> <p>-----</p> <p><i>I: “What do you think motivates us to feed into hopes and to, couch things you said and to cushion things. What is driving that?”</i></p> <p><i>H12: “I think part of its compassion, you never want your words to hurt. I suspect that part of it is our own discomfort with these situations, right? We're a culture where death and dying and cancer are all very negative words. And so, anytime you can skirt around those words, I think it does something for us as well. So that's my sense is we're always trying to soften that blow. But</i></p>

sometimes you wonder if that effort is not fair because there are some families who get to the end and say, 'I didn't realize that we were gonna get here' (Staff Physician, H12)

"I think the way that health care providers talk about goals of care and talk about what to be hopeful for really can influence what families are thinking are goals of care and where our hope resides. And so, I think they're entangled. It's like a Venn, probably not totally overlapping, because, as I say, the part of the Venn that's the hope for a miracle in most instances for a family would be larger than for a health care professional who maybe has both evidentiary and anecdotal experience of how things usually work out in a given context, but yeah, I think they're totally entangled." (Staff Physician, H16)

"There are some families who have made it clear, 'I don't want to talk about this. I've got one kid who's dying at home, who the parents have done everything possible to stay away from the hospital. We'll call them, but they won't answer the phone. We know they're around. And then every month or so, they will check in. But they're really controlling that, (pauses) face time with us. Maybe it's too hurtful. It's almost difficult with them to know exactly what it is that's done that 'cause this is actually a family that was very engaged during curative therapy. That's probably a family that if there was some kind of study, I might be a little reticent to present it to them.'" (Staff Physician, H12)

Ethical Tensions in Decision Making

<p>Ethical tensions</p>	<p>Believing that EOL trial enrollment would lead to suffering <i>"The situation that I was describing is- and that's not uncommon. It's a child who is, suffering and having disease that is progressive, metastatic, whatever. And conventional chemo(therapy), conventional radiation is just not working anymore. And for that reason, wanting to try everything and wanting to provide extra therapeutics, the phase one/phase two trials come into place. And, you know, obviously we don't know if they're going to work or not 'cause it's a phase one/phase two trial (laughs). And that is being discussed and being offered. Now, moral distress arises when those decisions are viewed by other members of the health care team as not appropriate. And by not appropriate, sometimes that comes down to, whether the nursing team, whether the trainees, whether the other staff taking care of the child, whether it's the social worker, the physiotherapists, pharmacists, are viewing that intervention as a source of prolonging suffering, where the focus should be on comfort care. So, that is where moral distress arises"</i> (Oncology Fellow, H15)</p> <p>Worrying about parental understanding of trials <i>"When you tell a family there's...I don't know how you communicate it, but do you tell a family there's a curative option? Or do you tell them there's a (pauses) needle in a haystack? Like there's another step that you can take, but really? Like it's not even possible. It would be beyond, beyond, beyond a miracle if it was successful. Versus a curative option. And I think there's an impulse to pursue treatment, especially in hem/onc [sic], no matter the odds of success, right? And there's always a(n) impulse for parents. Parents will always pursue treatment, no matter the odds of success, because that's their</i></p>
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	<p><i>job, right? That's innately what they're- it's their child. So, I think the way we communicate the limitations of the options versus balancing that impulse to push no matter the odds, is inevitably, can lead to more suffering. And I think in that cycle, what causes me, I think, the moral distress, is in the end, it deprives families of proper closure. Because the conversations that potentially should be had before the crisis, aren't had." (Social Worker, H32)</i></p> <p>Believing that a child's role in decision making is insufficient <i>"I think that's something that causes me some distress, often when I feel like we're doing something for the parent, but is that what the child would want? Or is that something they've discussed with the child and they're reflecting that in their decisions? It's something I think about a lot, is how does the kid feel about this? Or do they even know why we're making these decisions on their behalf?" (H31, Nurse)</i></p>
<p>Conflicting ethical principles in decision making</p>	<p>Autonomy vs beneficence and non-maleficence <i>....it doesn't feel like shared decision-making if you're not even presenting an option. It feels like paternalistic medicine.....most of us who were trained in North American medical systems in recent years feel like we have had it drilled into us that shared decision-making is the best decision-making model....to not offer something, feels paternalistic and wrong. But I also think it's really hard because, again, going back to if, a family's always going to choose intervention, even if you think that the harms potentially outweigh the benefits. (Staff Physician, H5)</i></p> <p>Parental vs child autonomy <i>..... are we just being unreasonable to this poor child about giving them one therapy after the other after the other? Because I think, the heart of that is the challenge of ultimately, our responsibility is to act in the best interest of the child. But what do we do when we've also got to look after the best interests of the family, the parents? And what do we do when we feel like the best interest of the parents is not the same as the best interest of the child?I think that's when it really gets tricky, that sort of balance between when the medical team feels 'Enough is enough. We need to focus purely on symptom care', but the family isn't there. I think that's the most difficult time. (Staff Physician, H13)</i></p>

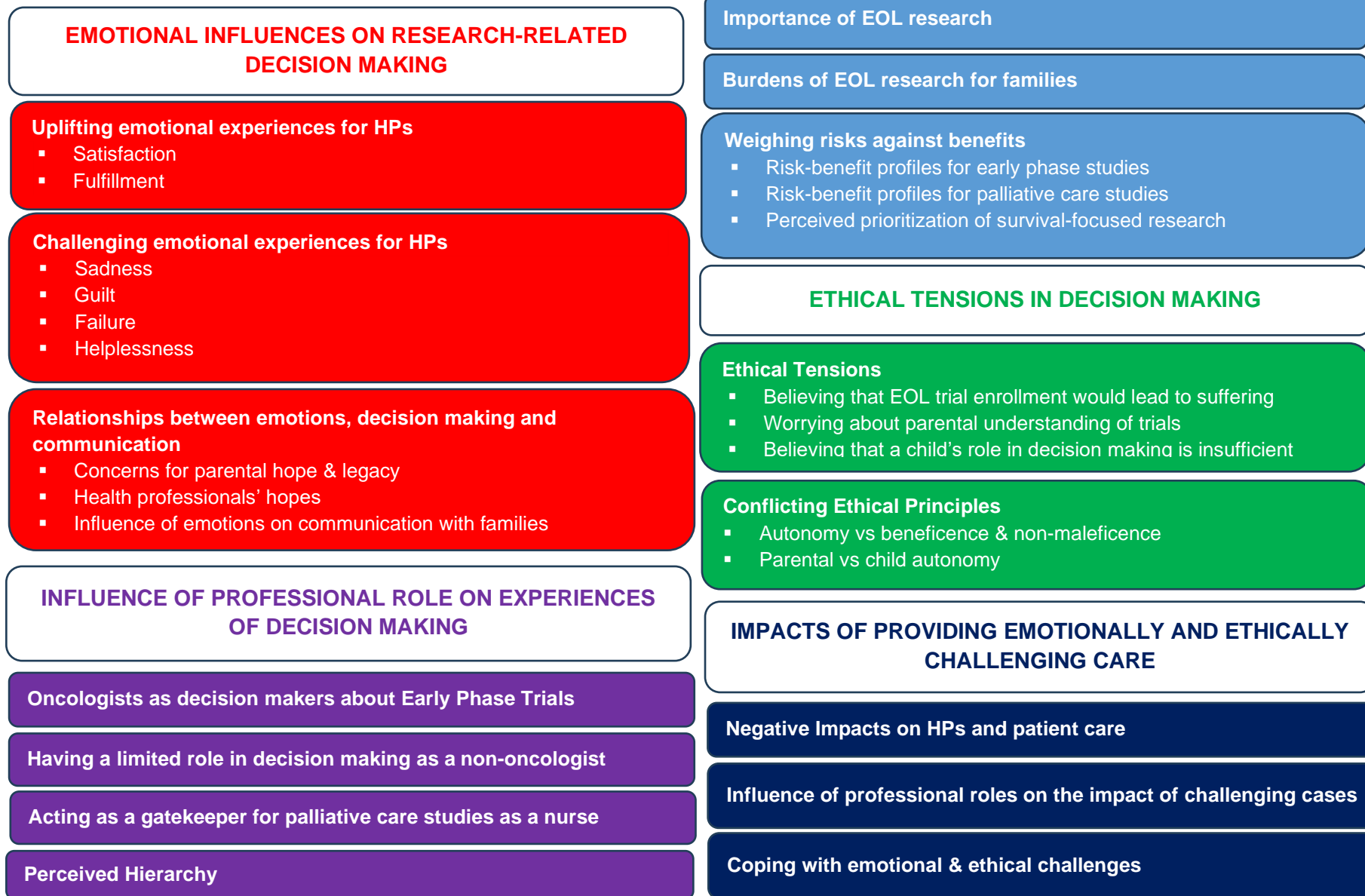
Influence of Professional Role on Experiences of Decision Making

<p>Oncologists as decision makers about early phase trials</p>	<p>H19: <i>“I do feel like the plan is made by the physicians, but I do feel we can question, but I don't know that we would stop it (pauses). There's open discussion though, in our team I feel.</i></p> <p>I: <i>So, a couple of the other participants have been talking to me about hierarchy in decision-making and that being something that has good sides and bad sides. Does that ring true with you?</i></p> <p>H19: <i>Yeah, (pauses) yeah, I do think they're open and we can talk about it, but I do think in the end, (pauses) you know, it's decided by the physicians. But someone has to make that decision, right?” (Nurse, H19)</i></p> <p>-----</p> <p><i>“I think when we're in these very challenging family situations and I'm thinking about, the few patients we've had where, probably antineoplastic therapy's not the right decision, but we're pursuing it because the family feels very strongly about it. Especially in those cases, it's very important to have the wider team's input and, I don't want to say buy-in because that sounds like we dictate and they have to listen, but at least we have group conversations. And I think we've gotten a little bit better at that over the years. I would say in the beginning, it was kind of like, well, we make the decision (laughs) at (name of subspecialty) rounds and everyone has to just do what we've decided. But overtime, it has become more multidisciplinary.” (Staff Physician, H9)</i></p>
<p>Having a limited role in decision making as a non-oncologist</p>	<p><i>“I think for me as a social worker I tend to have to take a back seat in a lot of these things (referring to conversations about decision making) because I'm not a medical professional. And there's some conversations we're privy to, and some conversations we're not.” (Social Worker, H32)</i></p>
<p>Acting as a gatekeeper for palliative care studies as a nurse</p>	<p><i>“I think some families are just <u>overwhelmed</u> and, you know, me saying it's too much today or they just want to go home. Today is not the day for extras and stuff”. I do think that it is good. Our families are here a long time, for years a lot of them, and it's tiring, and you can see it, the fatigue” (Nurse, H19)</i></p>
<p>Perceived Hierarchy</p>	<p>I: <i>“You talked about not being given permission to have certain conversations or to bring up certain options and you mentioned that, sometimes there are backroom conversations. So, you might have a conversation with the nurse about what happened, but it was to do with what the physician had said. I was wondering, is this a hierarchical thing? Does hierarchy come into who's allowed to say what?</i></p> <p>H32: <i>(Pauses) “Potentially. I don't think it's intentionally hierarchical. I think it starts with (pauses) (looking up, audible out-breath). I think it's because (pauses) the primary physician or the staff physician has to be comfortable to have that conversation and support that. So, if they're less inclined to have those conversations with families or less skilled or confident, or for whatever reason that for them, then it makes it more difficult for everyone else to have those conversations. But I would think if you're working with a physician that</i></p>

	<p><i>has more of a palliative background, that is more comfortable with that training and (a) much more open conversation.” (Social Worker, H32)</i></p>
<p>Impacts of Providing Emotionally and Ethically Challenging Care</p>	<p>Negative Impacts on HPs and patient care <i>I: “You mentioned differences of opinion about the best thing to do for a child. Can you tell me how that plays out?”</i></p> <p><i>H5: “I think some of it ends being backroom conversations. If there's a primary doc [sic] that makes a decision that other people disagree with, there becomes a narrative around other care providers on the ward or the nursing staff that isn't necessarily shared with that individual.”</i></p> <p><i>I: “What do you think is the impact of these backroom conversations?”</i></p> <p><i>H5: “I don't think it's good for team dynamics. I think it's better for us to communicate face-to-face. I also think it can lead to some moral distress in teams if you feel like the type of therapy we're pursuing is not in the best interest of the child. But I think that can be challenging for them that are actually involved with delivering the therapy that they might not agree with. I think it can lead to frustration and burnout.” (Staff Physician, H5)</i></p> <p>Influence of professional roles on the impact of challenging cases for HPs <i>“I understand why people were struggling with it (giving chemotherapy to a child close to the EOL). I think cause, you know they ha(d) to go home and know that they gave something that. The child ended up passing right after, so I feel like a lot of people would have struggled with that being like ‘did I administer that and then cause this?’I think it's hard for nurses 'cause you have to go home and know that you were the one providing the care, so people become morally distressed with its effects..... You're in the room every single hour, so you see problems bigger than other people see them just because, it's every single time you go in the room you're feeling something. The nurses share with each other because it's like, ‘well, you guys have been in there do you experience the same thing?’. So, I think that's why that happens because you can read through the notes and read why we're doing this, and the conversations, but if you're not present for them and then you're going in the room and you're feeling distressed about something every time you go in.” (Nurse, H34)</i></p> <p>Coping with emotional and ethical challenges <i>“The challenge is, sometimes you are not always in agreement with what the parents want and (pauses) you are challenged because you don't feel that you are doing a good job. You want to be on the child's side, but I have seen kids who died in the ICU despite (looking down, shakes head), you know, the fact that we knew that this was a bad decision. That's always something, you have to distance yourself from some of the decisions and not be too emotional, but it's really one of the challenges we face.” (Staff Physician, H28)</i></p>

Abbreviations: I: Interviewer, H indicates the participants unique study identifier, ICU: Intensive Care Unit

Figure 4.1. Categories, themes, and subthemes



Chapter 5

Conclusion

5 Conclusion

In writing this thesis, I sought to address important gaps in our knowledge about research participation involving children with cancer towards the EOL. I conceptualized EOL research as being two major groups of study: early phase studies of anticancer therapies, and a broad group of palliative and supportive care research studies. In my first paper, I used a population-based registry to identify the proportion of Canadian children who participated in early phase studies towards the EOL, and to describe this patient group. My second paper was a systematic review of the literature describing children's, parents', and HPs' perspectives about EOL research. Finally, the third paper was a qualitative study, further exploring HPs' perspectives about EOL research.

This chapter includes five sections. In the first section, I will describe whether I was able to meet the aims for each of the three papers. In the second section, I will describe the contribution that this thesis makes to pediatric oncology. In the third section I will discuss some key methodological considerations. In the fourth section I will highlight some areas for future study, before concluding with a fifth section that summarizes the thesis findings.

5.1 Were the Objectives Met?

5.1.1 Chapter 2

The aim of this chapter was to describe the population of Canadian children with cancer who participated in early phase trials towards the EOL. Specifically, I sought to describe the proportion of children who participated in studies and to describe the relationships between patient's demographic, disease and treatment-related characteristics and participation. Finally, I aimed to describe the EOL course of study participants and the trials they took part in.

Using 20 years of Canadian data from the CYP-C database, I identified that 4.5% of children participated in trials within their final 90 days of life. Trial enrollment began during this 90-day period for 40% of these children. Study participation was associated with a higher socioeconomic status, a brain tumor diagnosis, having previously registered on a clinical trial and being treated in a major early phase study center. Enrollment in early phase studies typically involved treatment with conventional chemotherapy agents. For patients who were enrolled in studies during the EOL period, hospitalization was uncommon, as were grade 3 or greater adverse events. Non-completion of treatment plans was common but only rarely due to toxicity.

5.1.2 Chapter 3

The purpose of this systematic review was to describe the perspectives and experiences of children, their parents, and the HPs who care for them about research studies where the participants are children with cancer towards the EOL.

I included 24 papers in the review, which described the perspectives of at least 1787 participants. Only one of these papers described perspectives about palliative care research, the remainder were focused on participation in early phase anticancer treatment studies. I identified eight themes in the published literature: ‘Seeking control’, ‘Faith, hope and uncertainty’, ‘Being a Good Parent’, ‘Helping Others’, ‘Barriers and Facilitators’, ‘Information and Understanding’ and ‘Role of HPs in Consent and Beyond’.

5.1.3 Chapter 4

In my final study, I sought to build on the literature described in the systematic review. Specifically, I set out to provide a richer description of HPs perspectives and experiences of EOL research. I included both physician and non-physician HPs to explore similarities and differences in HPs experiences across professional roles, and to learn about how decisions are made within teams. Finally, I aimed to compare perspectives about palliative care and early phase research.

My findings indicated that while HPs believed that EOL research was important, they worried about the implications of participating for children involved. They struggled with a minority of

situations where they perceived children were at risk of suffering due to research participation, or that children's wishes were not being incorporated when decisions were made about research participation. Many of the struggles that HPs experienced could be characterized as dialectical tensions, in particular, the struggle between allowing parental autonomy and protecting children from the consequences of parental decisions. HPs who implemented decisions without being involved in making those decisions particularly struggled with ethically challenging situations. Whereas HPs conceptualized early phase studies as treatment options as well as research studies, palliative care studies were primarily seen as research. Concerns about the methodology and scientific benefits of experiential and qualitative palliative care studies may have influenced HPs to gatekeep when researchers tried to recruit study participants.

5.2 Contribution to the Pediatric Oncology Literature

This thesis adds to the literature on the topic of children's participation in cancer research towards the EOL. This is an important area of study given, i) the contribution of cancer research to improving the care of future patients with cancer, ii) the potential implications of research participation for the children involved and their families at the EOL, and iii) the impact of providing ethically challenging care for the HPs involved.

Despite the significance of this topic, I am unaware of any population-based studies describing the epidemiology of the patient population that participates in early phase studies at the EOL. By performing this retrospective review, I was able to provide a detailed description of the Canadian population of study participants and of the trials that they participate in. In exploring the factors associated with participation, I identified possible barriers to participation. Addressing these potential barriers may help ensure more equitable access to study participation for children across Canada.

Similarly, I have not identified any other systematic reviews that specifically explore perspectives around EOL research participation for children with cancer. In performing my systematic review on this topic, I identified gaps in the previous literature, including a lack of depth in the description of HP perspectives, poor representation of non-physician HPs in the

published studies, a failure to describe how decisions are made, and a paucity of literature on palliative care research.

In my third, qualitative, study, I chose to focus on some of the knowledge gaps identified by the systematic review. This study gives light to some of the challenges faced by HPs who believe in the importance of research for the field of oncology but feel concerned about the possible impact that study participation may have on the children involved, at a time when they consider those children to be at their most vulnerable. These HPs found a small proportion of the cases that they were involved in to create significant tensions that at times resulted in moral distress and contributed to stress and burnout. This study also identified important tensions that occur in teams when communication about EOL decisions about research participation is suboptimal. HPs described situations where some team members felt that they were obliged to implement decisions without understanding how and why decisions were made and whether decision making had occurred in ways that they would have considered to be ethically appropriate, with truly informed consent. This may have a detrimental impact on the functioning of interprofessional teams, reducing their abilities to function effectively, and having broader negative impacts on care provision.

5.3 Methodological Considerations

There are several methodological issues that should be acknowledged when considering this thesis in its entirety.

First, there is no universal agreement on when the EOL period begins. The definition of EOL used for the first study differed from that used for the final two studies. For the purposes of the retrospective cohort study, it was necessary to choose a precisely defined timepoint for EOL. I chose 90 days to align with typical early phase trial inclusion criteria.

With regards to the second (systematic review) and third (qualitative) studies, participants were asked to describe perspectives and experiences of decision making during the period when children with poor prognoses were expected to only have months left of life expectancy. Since the date of death is only known in retrospect, EOL could not be defined in the same way as for

the quantitative study. For the systematic review, I included studies that implicitly or explicitly referred to a population of children who were no longer considered to be curable by conventional therapeutic options and who were thought to be in their final months. For the purposes of the qualitative study, I used a similar definition to the review, using conversation with participants to explore how they felt decision making changed for children with a poor prognosis as they approached their final months of life to understand the specific issues around research at EOL.

Second, while I chose to focus the topic of this thesis on EOL research, there is no standard conceptualization of, nor definition of, EOL research. Given an absence of any data collected regarding participation in palliative care research studies, the retrospective cohort study was narrowly focused on early phase studies of anticancer therapies. In the subsequent two studies, I was able to widen the definition of EOL research to include palliative care research, with this broad group including studies addressing issues like communication, decision making, care preferences, symptoms and their management. Given the rarity of these studies, there was only a single palliative care study included in the systematic review. With regards to the qualitative study, some participants needed clarification on what was meant by palliative care research, before they could comment on this type of study. Furthermore, a lack of palliative care studies that are conducted in practice, may have limited some participants' experience with this type of research. However, with explanation of the type of research that was included in my definition, participants were able to describe their own perspectives.

5.4 Future Directions

This thesis highlights several areas that warrant further study. The systematic review sought to describe the perspectives of children with cancer on research participation. However, children represented only a minority of the participants whose opinions and experiences were described in the review. Given the potential implications of research participation for the children involved, and the concerns that HPs expressed regarding children's rights to autonomy, it is important to understand children's own perspectives on this topic. Future research should explore how this can be done in an ethical way that is sensitive to children's emotional needs. However, given the concerns that HPs expressed regarding children's participation in research and their descriptions

of gatekeeping practices, I anticipate that this would be challenging to conduct. It has previously been suggested that palliative care research studies should incorporate surveys or other measures to assess the burden of research for participants^{122,147}. Incorporation of these measures in palliative care (and non-palliative care) research studies involving children may help to demonstrate that these studies can be conducted without causing harm and provide ongoing guidance on how studies can be performed in ways that are participant-friendly. As we learn more about the impact of research on children, these findings should be shared with the HPs caring for them. This may help to address recruitment challenges.

Many other findings of this thesis point to a need for interprofessional discussion and education regarding EOL research. For example, my quantitative study demonstrated that toxic deaths were uncommon among children on early phase trials, as was time spent in hospital at EOL. Sharing this information with nurses and other HPs caring for patients on trial, may reassure them and reduce levels of concern and moral distress. Interprofessional discussion may also provide a useful forum to discuss some of the benefits that parents and children find in research participation, as described in the systematic review. Additionally, where there are situations that cause emotional distress and ethical concern, bringing together decision-making and non-decision-making HPs, may create a setting for sharing those concerns and improve communication and shared understanding across disciplines. Beyond discussion and sharing of experiences, it is important that we also explore ways to incorporate team perspectives when decisions are made and find better ways to share and document how and why decisions have been made in the context of large teams.

The qualitative study highlights significant ethical tensions in EOL decision making that arise in a small number of cases. These cases center on ethical issues where parental rights to make decisions for their own children appear to conflict with HPs' perceptions of children's best interests, and/or HPs' perceptions of children's wishes. In our current model of family centered pediatric care, and in a medical and societal culture that values individualism and personal autonomy, it is seen to be appropriate that parents are given decision making authority over their children where children are unable to make decisions on their own behalf. However, HPs concerns that children could die whilst suffering because of parental decisions raise the question of limits to parental autonomy, and where these limits should lie. This question lies outside of the scope of this thesis but is an important issue to address in research and policy.

In exploring patterns of early phase study recruitment at the EOL, I identified that certain factors may act as barriers to research participation, including sociodemographic factors, like income, and location of care in a center without access to a broad range of early phase studies. I suggested that these barriers should be explored and addressed in the name of equity, for example by the introduction of financial and logistical supports to help families access trials. This may seem strange in the context of the subsequent papers in this thesis describing ethical issues related to children's participation in studies at EOL. I would argue however, that a more nuanced conclusion is that EOL research participation occurs in a wide variety of contexts. In some situations, research participation aligns with the goals and values of the participating children and families, and children participate without detrimental impact on their care and comfort at EOL. In other cases, study participation may have negative effects. If early phase trials are to be provided to patients with cancer including those at EOL, it is important that access to trials is equitable. It is clear from this thesis that EOL decision making about research is complex for the individuals concerned. Future work should explore how those individuals can be supported through decision making, and how we can improve decision making processes, so that decisions can be made that are tailored appropriately to the children and families concerned.

5.5 Conclusions

To summarize, this thesis demonstrates that a small proportion of Canadian children who die of cancer participate in early phase research studies of anticancer therapies towards the EOL. Patterns of study enrollment suggest potential barriers to participation. HPs perceive participation in early phase and palliative care research studies to be important for the field of oncology but worry about the implications for children whom they consider to be vulnerable. HPs experience dialectical tensions in caring for children on studies in situations that they perceive as ethically challenging. Ethical issues typically concern conflicts between parental rights to autonomy and HPs desire to protect children from harms of trial participation. Experiences of ethically challenging care may be associated with experiences of burnout and moral distress. Future work should explore ways to ensure that access to studies is equitable, but also focus on how to support children, families and HPs making these complex decisions.

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Appendices

Appendix A. Supplementary Information for Chapter 2

Supplementary Table 2.1. Univariate logistic regression describing relationship between predictor variables and enrollment in an early phase study, stratified by source database (POGONIS and CYP-C). This excludes 47 patients represented in both POGONIS and CYP-C databases.

Characteristic	Number of Deaths n=1508	OR	95% CI	Number of Deaths n=1570	OR	95% CI
Source Database	POGO			CYP-C		
Age at death	1508	1.00	0.95, 1.05	1570	1.01	0.97, 1.05
Sex						
Male	848	-	-	848	-	-
Female	660	1.12	0.65, 1.91	722	0.68	0.42, 1.07
Race						
White	739	-	-	1,032	-	-
Non-White/Mixed	307	1.35	0.69, 2.55	391	0.93	0.53, 1.55
Not Available/Other	462	0.82	0.42, 1.56	147	1.04	0.45, 2.12
Dwelling at First Diagnosis						
Rural	226	-	-	342	—	—
Urban	1271	0.93	0.47, 2.04	1220	0.91	0.55, 1.58
Income Quintile						
3-5 (higher)	870	-	-	962	—	—
1-2 (lower)	609	0.67	0.37, 1.16	590	0.39	0.22, 0.67
Last Cancer Diagnosis						
CNS	499			579	—	—
Leukemia & Lymphoma	458	0.67	0.34, 1.28	421	0.77	0.44, 1.32
Solid Tumor	551	0.63	0.33, 1.18	570	0.62	0.36, 1.04
Metastasis at Last Cancer Diagnosis						
Non-Metastatic	846	—	—	936	—	—
Metastatic	522	0.80	0.43, 1.4	613	0.64	0.39, 1.03

History of relapse before EOL						
No	951	—	—	1078	—	—
Yes	557	1.39	0.81, 2.38	492	1.10	0.68, 1.75
Time from First Diagnosis to Death	1508	1.01	0.88, 1.13	1570	0.98	0.85, 1.11
History of Cellular Therapy before EOL						
No	1192	—	—	1261	—	—
Yes	316	0.92	0.45, 1.73	309	0.85	0.45, 1.48
History of Radiation before EOL						
No	770	—	—	833	—	—
Yes	738	1.52	0.89, 2.64	737	2.23	1.41, 3.61
Number of Trial Enrollments before EOL	1508	2.58	1.92, 3.45	1570	3.36	2.54, 4.47
Initial Treatment in a Major Early Phase Study Center						
No	627	—	—	1254	—	—
Yes	880	1.99	1.12, 3.75	316	3.27	2.06, 5.16

Abbreviations: CI - Confidence Interval; CNS – Central Nervous System; CYP-C – Cancer in Young People in Canada Database; EOL – End of Life; OR - Odds Ratio, POGONIS – Pediatric Oncology Group of Ontario Networked Information System

Appendix B. Supplementary Information for Chapter 3

Supplementary Table 3.1. Database Search Strategy. Search initially performed on April 12th, 2017, then updated on August 19th, 2020.

Database [Platform] Searches run April 12, 2017	Results
MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE(R) Daily and MEDLINE(R) 1946 to Present [Ovid]	2,928
Embase Classic+Embase 1947 to 2017 Week 15 [Ovid]	4,081
PsycINFO 1806 to April Week 1 2017 [Ovid]	295
[Web of Science] Science Citation Index Expanded (SCI-EXPANDED) --1900-present Social Sciences Citation Index (SSCI) --1956-present	2,889
CINAHL [EBSCOhost]	270
TOTAL	10,463

Ovid MEDLINE Database Search Strategy:

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	Clinical Trials as Topic/ or Clinical Trials, Phase I as Topic/	190009

2	((("Phase i" or "Phase I") adj3 (trial or trials or study or studies or research)) or ((clinic or clinical) adj2 (trial or trials or study or studies or research))).tw,kf.	526815
3	1 or 2	658194
4	exp neoplasms/	2988852
5	(cancer* or carcinom* or hartoma* or leukem* or malignan* or neoplas* or oncolog* or paraneoplas* or sarcoma* or tumor* or tumour*).tw,kf.	3047582
6	4 or 5	3816350
7	limit 6 to "all child (0 to 18 years)"	406245
8	(infan* or newborn* or "new born*" or neonat* or baby* or babies or toddler* or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child* or adolescen* or juvenil* or youth* or teen* or "under* age*" or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).mp. or school*.tw.	4104485
9	6 and 8	484930
10	7 or 9 [cancer and children]	484930
11	3 and 10 [clinical trials and children with cancer]	16625
12	attitude/ or "attitude of health personnel"/ or attitude to death/ or attitude to health/ or health knowledge, attitudes, practice/ or optimism/ or pessimism/	310924
13	Perception/	27534
14	Motivation/ or Intention/	65785
15	"Referral and Consultation"/	59839

16	Therapeutic Misconception/	101
17	Communication/	74126
18	Decision Making/ or Choice Behavior/	106155
19	Comprehension/	11183
20	(aspiration* or attitude* or belief* or communicating or communicated or comprehen* or decide* or decision* or disincentiv* or expectation* or goals or incentiv* or intent or intention* or judgement* or misconceive* or misconception* or misunderstand* or misunderstood or motivat* or perception* or perspective* or purposes or reason or reasons or referral* or understand* or understood or view or views or wish or wishes).tw,kf.	2954083
21	or/12-20	3235583
22	11 and 21 [attitude about clinical trials and children with cancer]	3147
23	limit 22 to english language	2928

Supplementary Table 3.2. Comprehensiveness of Reporting of Included Qualitative Studies

Quality Criterion					References								%	
					36	91	85	37	38	148	84	39		86
Research Team and Reflexivity														
<i>Personal Characteristics</i>	Names of interviewers are stated				X		X		X	X				36.4
	Credentials of interviewers are described				X									9.1
	Occupations of interviewers are described	X	X		X									27.3
	The experience and training of interviewers are described		X						X	X				27.3
<i>Interviewer Relationship with Participants</i>	Any prior relationship (or lack thereof) between participants and interviewers are described													0
	The interviewers' personal interest in the subject discussed is disclosed													0
Study Design														

<i>Theoretical Framework</i>	The methodological orientation and theory behind the study is disclosed				X		X ²						18.2
<i>Participant Selection</i>	Sampling methods are discussed	X			X			X	X		X		45.5
	Method of approach is discussed		X		X		X		X	X			45.5
	Sample size is stated	X	X	X	X	X	X	X	X	X	X	X	100
	Information is provided on those who refuse participation	X		X				X	X			X	45.5
<i>Setting</i>	Setting of data collection is discussed		X	X	X			X			X		45.5
	Presence of non-participants during interviews is mentioned	X									X		18.2
	A description of the study sample is provided	X	X	X	X	X	X ³	X	X		X	X	90.9
<i>Data Collection</i>	It is stated whether an interview guide was used	X	X	X	X	X	X	X	X	X	X	X	100
	and pilot tested	X		X ¹	X	X			X			X	54.5

	It is stated whether repeat interviews were conducted				X			X	X	X	X		45.5
	It is stated whether audio or visual recording occurred	X	X	X	X		X	X	X	X	X		81.8
	It is stated whether field notes were taken		X										9.1
	The duration of interviews is discussed		X		X						X		27.3
	The authors note whether they sampled to data or theoretical saturation		X		X								18.2
	It is stated whether transcripts were returned to participants		X								X		18.2
Analysis and Findings													
<i>Data Analysis</i>	The number of coders is mentioned	X		X		X	X	X	X	X	X	X	81.8
	The coding tree is described or provided						X						9.1
	The authors state whether themes were derived <i>a priori</i> or inductively	X	X	X	X	X	X	X	X	X	X	X	100

	It is stated whether data analysis software was used		X		X		X	X	X				45.5
	It is stated whether participant checking occurred		X		X					X			27.3
<i>Reporting</i>	Quotations are presented	X	X		X	X	X	X	X	X	X	X	90.9
	The quotations are contextualized								X			X	18.2
	Data and findings are consistent	X	X	X	X	X	X	X	X	X	X	X	100
	Major themes are presented	X	X	X	X	X	X	X	X	X	X	X	100
	Minor themes and diverse cases are discussed clearly	X	X	X	X	X	X		X		X	X	81.8

‘%’ is the percentage of studies reporting the item.

X¹ Although the interview guide was not piloted, it had been developed and previously been used by the same authors in several previous pediatric oncology studies¹⁴⁹⁻¹⁵¹.

X² Limited information is provided about methodological orientation.

X³ A description of the study sample was not provided in order to protect the anonymity of the small group of participants.

Supplementary Table 3.3. Included Survey-Based Studies: Quality Appraisal

Quality Criterion	Reference											%
	41	94	88	19	42	40	92	95	80	87	81	
Research Question and Study Design												
A survey was the most appropriate method to study the specific research question	X	X	X	X	X	X	X	X	X	X	X	100
The survey had been previously shown to be reliable and valid. If not, there were no other reliable, validated surveys that could have been used	X ¹	X ¹	X ¹	X ⁴	X ¹	X ¹	X ¹	X ⁸	X ¹	X ¹	X ⁷	100
Consumer views were incorporated into survey design, distribution, and administration								X ⁵	X ⁵			18.2
Format												
The survey title was appropriate	X					X						18.2
The use of open and/or closed questions was appropriate	X		X		X	X	X	X	X		X	72.7
Non-threatening questions were placed at the beginning of the measure and sensitive ones near the end	X					X			X		X	36.4

The survey was brief	X				X	X			X		X	45.5	
The questions were clear enough to be understood by participants	X					X				X	X	36.4	
Instructions to participants													
The survey contained adequate instructions for completion	X					X					X	27.3	
Adequate instructions were provided on returning completed surveys (or surveys were submitted online)	X					X	X	N/ A	X ⁶			40	
Adequate explanation about the study was provided	X					X						18.2	
Piloting													
Survey was piloted in terms of method and means of administration, on individuals similar to the study population	X ²								X ²		X	X ⁷	36.4
Details were provided about pilot exercise	X											9.1	
Details were provided of how the definitive instrument changed as a result of piloting													
Sampling													

Sampling frame was sufficiently large and representative	X	X ³	X ³	X ³	X	X	X	X	X	X	X	100
Survey was suitable for all participants/potential participants (accounting for likely range of physical/mental/cognitive abilities, language/literacy, understanding of numbers/scaling, and perceived threat of questions or questioner)	X					X					X	27.3
Distribution, Administration and Response												
Appropriate methods were used to distribute the questionnaire	X			X	X	X	X	N/A	X ⁶	X		70
Appropriate methods were used to administer the questionnaire	X			X	X	X	X	X	X	X		72.7
Response rates were reported fully, including details of participants who were unsuitable to participate or refused participation	X		X		X	X	X	X	X ⁶	X		72.7
Potential response biases were discussed			X	X				X	X	X		45.5
Coding and Analysis												
Appropriate data analysis was performed	X	X	X	X	X	X	X	X	X	X	X	100
Results												

All relevant data appear to have been reported	X	X	X	X	X	X	X	X	X	X	X	100
Qualitative results were adequately interpreted (n=4)	N/ A	N/ A	X	X	N/ A	N/ A	N/ A	N/ A	N/ A	X	X	100
Adequately contextualized quotations are presented (n=4)	N/ A	N/ A		X	N/ A	N/ A	N/ A	N/ A	N/ A			25
Conclusions and Discussion												
The researchers have drawn an appropriate link between the data and their conclusions	X	X	X	X	X	X	X	X	X	X	X	100
The findings have been placed within the wider body of knowledge in the field and recommendations are justified	X	X	X	X	X		X	X	X	X	X	90.9

‘%’ is the percentage of studies reporting the item.

N/A Not applicable

X¹ No previously validated or reliable survey was available.

X² Limited piloting was performed.

X³ A convenience sample was used.

X⁴ Two surveys were used, one adapted from a survey that had previously been shown to be validated and reliable, one that had not^{152,153}. Neither adapted survey had been shown to be valid or reliable. However, no previously validated or reliable survey was available.

X⁵ Consumer views were incorporated into survey design but not distribution, and administration.

X⁶ Surveys were distributed in hard copy form at a conference and online. Limited information is available on the true sampling frame, and therefore the response rate. It is also unclear how paper surveys were to be returned or the instructions provided to participants.

X⁷ Although this survey was not piloted, nor studied to ensure it was valid or reliable, it had been developed and previously been used by the same authors in two previous studies of pediatric leukaemia^{111,154}

X⁸ This survey had been developed and previously been used by the same authors in several previous pediatric oncology studies^{10,103,155}

Supplementary Table 3.4. Included Case Series: Quality Appraisal

Quality Criterion	Reference		%
	90, 89, ,	50	
Were there clear inclusion criteria for the case series?		X	50
Was there consecutive inclusion of participants?		X	50
Was there complete inclusion of participants?		X	50
Was there clear reporting of the demographics of the participants in the study?		X	50
Was there clear reporting of relevant clinical information about the participants?		X	50
Was a clear description provided of the clinical setting for the study?	X	X	100
Was data analysis appropriate?	X	X	100

Appendix C. Supplementary Information for Chapter 4

Appendix C.1 Conceptual Framework of EOL Decision Making

This conceptual framework describes children, parents, and HPs as the key decision makers, making their decision within a broader socio-cultural and medical context. Although the findings of our systematic review of the pediatric literature did not discuss the broader context to pediatric EOL decision making (for example, wider socio-political and health system related factors), the Kim framework that we used as a basis for our conceptual framework cited these factors as being relevant¹²³. Since it is conceivable that these factors could influence decision making, we retained them in our revised framework.

Our revised framework describes how key decision makers communicate and exchange information so that decisions around EOL care can be negotiated. Key aspects of this process include practical aspects of giving and taking consent, information needs from the perspectives of families, and the roles of various participants including the child, parents, and HPs in this information exchange. The decision made (to participate or not in EOL research) is hypothesized to be influenced by (1) the personal characteristics of the decision makers, (2) their goals of decision making, (3) the available options and alternatives and their characteristics and (4) the broader social and medical context. Ultimately, a decision is made, with varying degrees of impact on the individuals involved.

Supplementary Figure 4.1. Thematic analysis of findings from our systematic review and three published conceptual frameworks, mapped onto a revised conceptual framework.

Our systematic review	Weaver, 2019	Schröder Håkansson, 2019	Kim, 2018	New conceptual framework
<ul style="list-style-type: none"> • <u>Seeking control</u> <ul style="list-style-type: none"> • wanting choices • trying anything • awareness of poor prognosis • <u>Faith, hope and uncertainty</u> <ul style="list-style-type: none"> • hope • uncertainty • faith • <u>Being a good parent</u> <ul style="list-style-type: none"> • fulfilling a ‘good parent’ role • acting in the child’s best interest • <u>Information and understanding</u> <ul style="list-style-type: none"> • practicalities of consent • honest clear communication • specific information needs • participant understanding • HP beliefs & understanding • <u>Role of HPs in consent & beyond</u> <ul style="list-style-type: none"> • trust, support, reassurance & guidance • training to take consent • impact on HPs • <u>Helping Others</u> <ul style="list-style-type: none"> • altruism • legacy • <u>Barriers/facilitators</u> <ul style="list-style-type: none"> • access to trials • burden of participation • familiarity & convenience • impact on HPs • <u>Involvement of the child in decision making</u> 	<ul style="list-style-type: none"> • <u>Benefits</u> <ul style="list-style-type: none"> • altruism & helping others • reflecting, reconstructing memories & creating meaning • being remembered • feeling included • sharing your story • therapeutic value of sharing • <u>Burdens</u> <ul style="list-style-type: none"> • absence of burden • inconvenient timing • fatigue • emotional strain 	<ul style="list-style-type: none"> • <u>Context</u> <ul style="list-style-type: none"> • Research integrated healthcare • <u>Concerns</u> <ul style="list-style-type: none"> • obtaining consent without straining the family • <u>Balancing values and obligations of healthcare and research</u> <ul style="list-style-type: none"> • adjusting to the family • safeguarding from psychological harm • introducing research & building trust • <u>Potential consequences</u> <ul style="list-style-type: none"> • authoritative or overprotective HPs • diminished family autonomy 	<ul style="list-style-type: none"> • <u>Healthcare system</u> • <u>Family, culture, values, uncertainty, autonomy</u> • <u>Communication of information & negotiation of decision</u> • <u>Characteristics of decision makers</u> <ul style="list-style-type: none"> • Self efficacy • health belief • psychological factors • emotional factors • desire of involvement • cognition • <u>Goals of decision making</u> <ul style="list-style-type: none"> • quality of life • hope • meaning • symptom control • good death • honor patient • family harmony • <u>Options and Alternatives</u> • <u>Outcomes of decisions</u> <ul style="list-style-type: none"> • regret • satisfaction • conflict 	<ul style="list-style-type: none"> • <u>Decision-making context</u> <ul style="list-style-type: none"> • broader societal context • healthcare system • research integrated healthcare • family context • <u>Decision makers</u> <ul style="list-style-type: none"> • child • parents (family) • HPs • <u>Communication of information & negotiation of decision</u> <ul style="list-style-type: none"> • information needs • practicalities of consent • role of HPs, parents and child • <u>Characteristics of decision makers</u> <ul style="list-style-type: none"> • psychological factors • emotional factors • desire to maintain control • awareness of prognosis • <u>Goals of decision making</u> <ul style="list-style-type: none"> • hope (avoiding false hope) • symptom control/quality of life • meaning (altruism/legacy) • being a good parent • family interests/harmony • <u>Options and Alternatives</u> <ul style="list-style-type: none"> • barriers/facilitators • burdens of participation • <u>Outcomes of decisions</u> <ul style="list-style-type: none"> • impacts on child/family • impacts on HPs

Appendix C.2. Supplementary Table 4.1. Members of the Research Team and their Roles in the Study.

Team Member	Background	Contribution to the Study
Fyeza Hasan	Oncology Fellow and PhD student with an interest in palliative care, specifically EOL decision-making. Received training in qualitative methods during PhD program.	(Student) principal investigator. Designed and conducted all study procedures (except transcription) including participant recruitment, interviewing, data analysis and interpretation. Wrote the manuscript.
Leeat Granek	Researcher with background in psychology, expertise in qualitative methods and an interest in pediatric palliative care.	Provided oversight and guidance regarding recruitment, interviewing and data analysis. Contributed to discussions about data interpretation and reviewed the manuscript.
Kimberley Widger	Nurse Researcher with expertise in pediatric palliative care and experience in qualitative research.	Provided oversight and guidance on design and conduct of the study. Contributed to discussions about data interpretation and reviewed the manuscript.
Angela Punnett	Oncologist, practicing in tertiary oncology center where early phase trials are performed. Has experience in qualitative research.	Provided oversight and guidance on design and conduct of the study. Contributed to discussions about data interpretation and reviewed the manuscript.

Sarah Cohen- Gogo	Oncologist, practicing in tertiary oncology center where early phase trials are performed. Runs an early phase trials program, managing patients on trial. Has an interest in pediatric palliative care.	Contributed to discussions about data interpretation and reviewed the manuscript.
Lillian Sung	Oncologist, practicing in tertiary oncology center where early phase trials are performed. Has an interest in supportive care for children with cancer and experience in qualitative research.	Provided oversight and guidance on design and conduct of the study. Contributed to discussions about data interpretation and reviewed the manuscript.

Appendix C.3. Participant Demographic Questionnaire

Children with Hard-to-Treat Cancer as Participants in Research

Thank you for taking the time to fill in this questionnaire

How do you describe your gender?

Please specify _____

Prefer not to answer

Which of the following categories best describe you?

Asian – East

Asian – South

Asian – Southeast

Black – African

Black – Caribbean

Black – North American

First Nations

Indian – Caribbean

Indigenous/Aboriginal (not included elsewhere)

Inuit

Latin American

Métis

Middle Eastern

White – European

White – North American

Other race/ethnicity (please specify) _____

Prefer not to answer

What is your professional role in the hospital?

Nurse

Nurse practitioner

Physician – Oncology

Physician – PACT

Social worker

Other (please specify) _____

In which parts of the Division of Oncology do you mainly practice? (Complete as many as apply).

Bone Marrow Transplant

Leukemia/Lymphoma

NeuroOncology

Solid Tumors

How many years of experience do you have working in pediatric oncology?

Please specify _____

(i) Does your current (or any previous) professional role include conducting research?

Yes

No

If answer to (i) is Yes, please complete (ii) and (iii):

(ii) Do you (have you) conducted research on the subject of palliative or end-of-life care?

Yes

No

(iii) Do you (have you) conducted research involving children receiving palliative or end-of-life care?

Yes

No

Appendix C.4. Semi-Structured Interview Guide

Introduction

1. My name and role at this hospital.
2. The aims of the interview – to try and understand the decision-making process that health professionals (HPs) undertake when deciding whether a child with cancer with a poor prognosis should take part in research.
3. A reminder that the interview will be recorded – they can choose to request no recording if they prefer, and I will make written notes instead.
4. A reminder that they can choose to skip a question if they prefer or stop the interview at any time.
5. An opportunity to ask questions before getting started.

Questions

1. Would you start off by telling me about yourself and your role in the hospital?
2. Can you tell me about the patients that you take care of?
3. Can you tell me about the aspects of your work that you most enjoy? What aspects of your work do you find challenging?
4. What are your thoughts and feelings about research where the participants are children with cancer who have a poor prognosis?

Possible prompts:

Importance of such research, benefits of this research, challenges of this research, What about children with no realistic chance of cure?

5. I'm specifically interested in research at the EOL. What would you consider to be EOL research? What are your thoughts and feelings about research where the participants are children with cancer approaching EOL?

Possible explanation:

When I talk about EOL research I'm talking about both early phase type research studies that involve anticancer treatments or what we might call palliative care research – (which could include studies about symptom management, decision making, perspectives about care). What do you think about those types of research?

Discuss different types of research depending on how the participant distinguishes between them

6. We've talked about several different types of EOL research, phase I and II studies that test anti-cancer drugs. We've also talked about palliative care research studies that don't test anti-cancer treatments, but may explore decision making, perspectives, symptom management etc.

Do you think that the risks and benefits of these different types of studies are similar or different?

Do you think these different types of research are valued equally by healthcare professionals?

7. Can you think back to a situation where the medical team was considering offering research participation to the family of a child with a poor prognosis cancer and who was coming towards the EOL?

Possible prompts:

Can you tell me about that situation?

Can you tell me about the family and the child?

What was your relationship like?

What kinds of things were you thinking about when you were/the team was making this decision?

How do you think your relationship with the family influenced the types of conversations you had with them? Are there other situations you can think of where that happened?

If they refer to family context, or coping – how did you know how they were coping?

Have you offered a research study and thought, maybe it wasn't the best option? Tell me what happened? What made you decide to offer it in the end? What do you do in that situation when you feel you have to offer something, but you're not sure it's the right thing?

Can you tell me about the decision-making process around offering research participation?

Possible prompts:

How did you (the team) come to make that decision?

What aspects did you (or the team) consider when making that decision?

What were the benefits and draw backs to offering this option?

Was this a difficult decision for you? What was difficult? What was the source of the difficulty?

Was this a typical case? What's different about a more typical case?

8. (If not covered earlier) When a child with cancer gets closer to the EOL what do you see as being the main benefits or risks of taking part for the child and their family?

Possible prompts:

We've talked about 2 main kinds of EOL research study. Does the type of the study influence the decision making in any way?

How do you present the risks and benefits? (Do you talk about clinical trials as being potentially curative or do they talk about extension of life, symptom reduction etc. Do you focus on an 80% failure rate or a 20% survival rate?)

What is the role of the health care team in helping the family make their decision?

Possible prompts:

What is your specific role?

What about shared decision making? What does shared decision making mean in this context?

Do families ever ask you what you would choose for your own child? How do you respond?

9. There are many different individuals involved in decisions about EOL research participation – the child, the family, the medical teams, the researchers, the hospital. Are there ever tensions between the child's and the families' interests?

Possible prompts:

How are the tensions resolved?

What about tensions between the need of the researcher to do research in a big institution vs the need of the child and family?

10. Is there anything else that you'd like to add? Is there anything more that I should know about?